STUDIES CONCERNING THE NATURE OF GRIGNARD REACTIONS WITH KETONES

A THESIS

Presented to

The Faculty of the Division of Graduate

Studies and Research

By

Thomas L. Wiesemann

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the

School of Chemistry

Georgia Institute of Technology

March, 1977

STUDIES CONCERNING THE NATURE OF

GRIGNARD REACTIONS WITH KETONES

Approved:

Chairman

Date approved by Chairman: 17 MAY 1977

ACKNOWLEDGMENTS

The author wishes to thank his advisor, Dr. E. C. Ashby, for his guidance throughout the course of this work. Dr. Ashby suggested these problems and his interest and enthusiasm were instrumental in their successful completion. The author also wishes to thank his co-workers, especially Jerry D. Buhler, Irene Lopp, Joseph S. Bowers and Joe T. Laemmle for their suggestions during many discussions concerning the work in this thesis. The author wishes to express his gratitude to his reading committee, Dr. H. O. House, Dr. D. S. Caine, and Dr. E. M. Burgess, for their suggestions during the first draft of this thesis.

The author has held NDEA and Union Camp Corporation fellowships for which he is grateful. Financial assistance by the Georgia Institute of Technology and the National Science Foundation is also gratefully acknowledged.

The author would like finally to acknowledge the encouragement of his wife, parents, and friends towards the completion of this endeavor.

TABLE OF CONTENTS

LIST OF TABLES

Table | Page

Table | Page

LIST OF ILLUSTRATIONS

SUMMARY

The reactions of methyl- and tert-butyl Grignard reagents with benzophenone, 2-methylbenzophenone (2-MBP), fluorenone and acetone were studied in an attempt to determine the influence of ketone reduction potential, solvent, magnesium metal purity and mode of Grignard preparation on the reaction mechanism.

The reaction of 2-MBP with methylmagnesium bromide was studied in detail. Methylmagnesium bromide prepared from magnesium samples containing significant amounts, ca. 20 ppm, of iron and other first row transition metals yielded substantial amounts of 2,2'-dimethylbenzopinacol at high Grignard to ketone ratios as well as normal addition products. Also, at low Grignard to ketone ratios, addition of catalytic amounts of iron and other first row transition metal salts to methylmagnesium bromide yielded large amounts of 2,2'-dimethylbenzopinacol. Multiple regression and correlation analysis shows a direct relationship between the amount of transition metal salt added to the Grignard reagent and the amount of pinacol formed. In reactions with 2-MBP, both erythro and threo pinacols were formed. The threo pinacol (isolated in substantial yield early in the reaction at low temperature) was shown to be the kinetic product which quickly converts to the thermodynamic erythro pinacol (95:5) at room temperature. A mechanism describing the transition metal catalyzed formation of pinacols is presented which is consistent with the known facts about this reaction. The formation of 2-methylbenzhydrol at high

Grignard to ketone ratios was found to be due to a minor amount, ca. 0.2% of a very reactive magnesium hydride species formed during the reaction of methylbromide with magnesium metal in diethyl ether. The relationship between the grade of magnesium used to prepare the Grignard reagent and the amount of 2-methylbenzhydrol formed was found to be due solely to the size of the magnesium crystals or turnings and the rate at which methylbromide was added to the magnesium.

The reactions of methyl, tert-butyl and allyl Grignard reagents with cis- and trans-2,2,6,6-tetramethylhept-4-ene-3-one ("cis- and trans-enone") were studied to further investigate the extent of single electron transfer (SET) in Grignard reactions in the absence of transition metal impurities. It appears that the reaction with t-butyl Grignard reagents is predominantly SET, while the reaction with allyl Grignard reagents is predominantly polar. The mechanism involved in the "enone" reaction with methyl Grignard reagents is questionable, but most of the evidence favors a polar more than a SET pathway. In light of the various possible situations which may be encountered in the "cis-enone" probe system, however, there is an alternate explanation. All of the reactions may occur via a SET pathway to give a radical cation-radical anion pair. In the case of "t-BuMgCl", collapse of this pair to give products must be slower than isomerization of the "cis-ketyl" to the trans isomer. In the case of "Allyl MgBr" the opposite must be true: collapse to give products must be faster than isomerization. In methyl Grignard reactions with "cis-enone", collapse of the ion pair to give products must be comparable in rate to ketyl isomerization. Similar arguments could be made for the reactions of Grignard reagents with aromatic ketones.

The formation of pinacol in Grignard reactions with benzophenones, and the isomerization of starting enone in Grignard reactions with "cis-enone" have been shown to be inhibited by the presence of 20-30% p-dinitrobenzene in most cases. This information was used to further investigate the mechanism involved in the 1,2-addition of methyl Grignard reagents to ketones.

CHAPTER I

INTRODUCTION

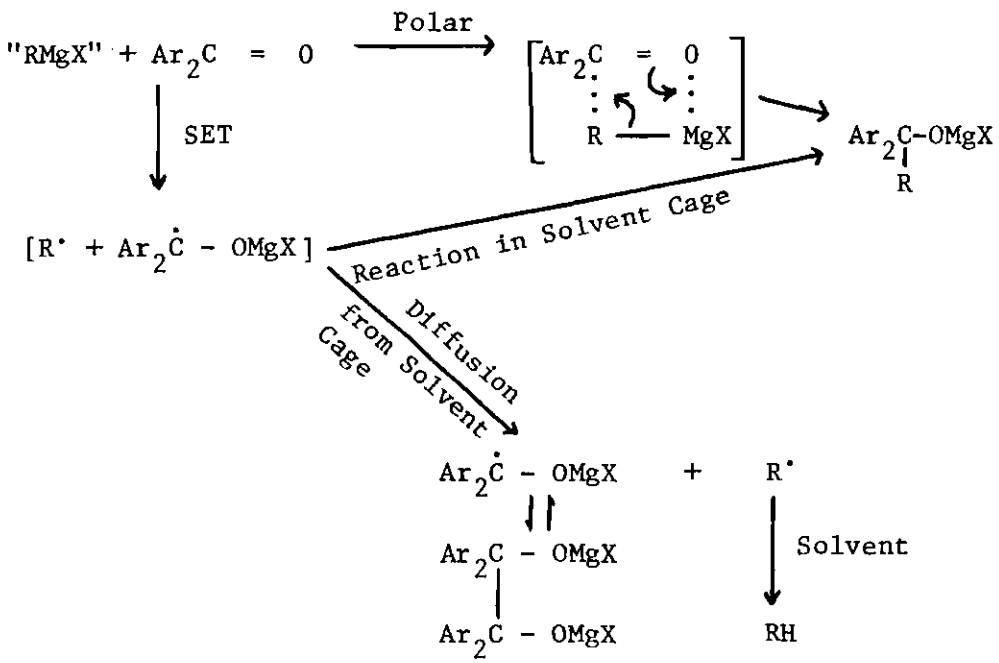
Modus Operandi

The research involved in this thesis was carried out as part of a team effort in the study of Grignard reaction mechanisms. In order to present a clear and complete story, it is necessary for me to include in this thesis some of the work carried out by other members of this team. In each instance proper acknowledgement will be given in parentheses. Most of the outside material is drawn from investigations made by Jerry D. Buhler. The rest comes from experiments carried out by Irene G. Lopp, Joseph S. Bowers, Joe T. Laemmle and Dan P. Campbell, who made up the rest of this team of investigators.

Background

The importance of the Grignard reaction in synthetic organic chemistry is well recognized; however, the mechanism whereby Grignard reagents react with organic substrates (and particularly ketones) is not well understood. The major areas of controversy over the years have been concerned with the nature of the Grignard reagent in solution, the designation of the reactive species, the kinetic order to the reactive organomagnesium species, and the nature of the alkyl transfer. Satisfactory solutions to the first three areas have been found;

however, the exact nature of alkyl transfer from the Grignard reagent to the ketone, whether it proceeds by a polar or a single electron transfer (SET) mechanism has been a source of considerable speculation. As a result of previous studies[1], this research group has discussed in detail the polar mechanism whereby methylmagnesium bromide ("CH_3MgBr") reacts with 2-methylbenzophenone[2] (2-MBP) and benzonitrile.[3] However, while this work was being carried out, evidence was presented by several other research groups to indicate that the reaction of Grignard reagents with ketones could and does proceed in some cases by a SET pathway.



(1)

Fauvarque has studied the reaction of R_2Mg compounds with fluorenone and benzophenone in various solvents.[4] His ESR observations indicate that ketyl concentration depends on the polarity of the solvent

and the ability of the alkyl group to stabilize the radical. Significant amounts of ketyl were observed when dibenzylmagnesium was allowed to react with fluorenone in HMPA; however, the same reaction in ether showed only a trace of ketyl to be present. Hydrolysis of the reaction mixture in HMPA gave only normal addition and reduction products for which Fauvarque proposed a SET mechanism similar to eq. 1.

Also in 1968, Blomberg and Mosher presented additional evidence supporting SET pathways in Grignard reactions.[5] In the reaction of "neopentylmagnesium chloride" with benzophenone in THF, not only did they observe 1,2-addition, but they also found benzopinacol and neopentane both in 20% yield. Presumably the neopentane arose from hydrogen abstraction of the solvent by a neopentyl radical. In this study, Blomberg and Mosher also reported observing an ESR signal which they assigned to the ketyl. From their data they drew a mechanism similar to that described by equation 1, citing both polar and SET pathways as operative in the reaction.

More recently, Holm and Crossland have presented convincing evidence for a rate determining SET step in the reaction of "t-BuMgCl" with benzophenone in diethylether.[6] In reactions with various substituted benzophenones, they obtained 1,2-addition products ranging from 0-55%, pinacol from 0-21%, 1,4-addition products from 0-39% and 1,6-addition products from 0-100%. For all of these reactions, however, the Hammett plot of relative rate versus σ-substituent constant gave a straight line (even when the substituted benzophenone had two or three ortho-methyl groups). In similar reactions using "CH_3MgBr" the presence of only one ortho-methyl group on benzophenone caused

significant deviation from the linear free energy relationship. Although, when added to acetone, "CH_3MgBr" reacts faster than "t-BuMgCl", Holm and Crossland have pointed out that "t-BuMgCl" reacts 100 times faster than "CH_3MgBr" towards benzophenone and 100,000 times faster towards the more sterically hindered duryl phenyl ketone. Based on this evidence, they proposed that the rate determining step for the reaction of "t-BuMgCl" with benzophenone involves SET to give an intermediate common to all products (similar to eqn. 1). The SET is then followed by one or more fast steps to give the observed products. On the other hand, they considered it likely that the reaction of "CH_3MgBr" with benzophenone proceeds through a polar pathway.

While carrying out kinetic experiments which established the first order dependence of the reaction of the Grignard reagent when "CH_3MgBr" was allowed to react with benzophenone, members of this research group made additional important observations.[2,3] They found that the amount of addition product observed compared to by-product (benzopinacol and benzyhydrol), as well as the observed rate constant, was dependent upon the ratio of Grignard reagent to ketone, the "purity" of the magnesium used to prepare the Grignard reagent, and the manner in which the Grignard was prepared (that is, using excess magnesium or excess methylbromide in the preparation).[7] This was interpreted to imply that an impurity catalyzed side reaction was taking place giving rise to the by-products in the reaction. The exact nature of this reaction was unknown.

Purpose

In light of these observations, it is felt that the nature of the solvent, ketone, R-group of the Grignard reagent, purity of the magnesium used to prepare the Grignard reagent, and mode of preparation of the Grignard reagent are all influential in determining the course of the reaction. The initial investigation of this thesis involves the influence of added transition metal salts on Grignard reactions with benzophenones in various solvents. The goal was to determine the influence of magnesium metal purity on the reaction pathway and to observe any effects due to solvent changes. This investigation was then followed by a detailed study of the reaction of Grignard reagents with benzophenone and 2-MBP. The objective of this study was to determine: (1) the nature of the side reactions giving rise to the by-products, (2) the nature of the impurities catalyzing these side reactions, (3) the extent (if any) of SET pathway operating in Grignard reactions when transition metal catalysts are rigorously excluded and, (4) the conditions which determine the extent of SET reaction.

An investigation was made of Grignard reactions with both fluorenone and acetone. The object was to examine the influence of the reduction potential and the nature of the ketone on the reaction pathway. In addition, a study was carried out utilizing both cis and trans-2,2,6,6-tetramethylhept-4-ene-3-one ("cis and trans-enone") as a probe. This was primarily directed towards a deeper understanding of the nature and extent of SET in Grignard reactions (goals (3) and (4) above). This study was expanded to include a variety of other metal and mixed metal alkyls in order to gain better perspective

regarding the nature of this probe.

CHAPTER II

EXPERIMENTAL

Materials

Solvents

Fisher reagent grade anhydrous diethyl ether was stored over sodium, then distilled under nitrogen from $LiAlH_4$ and/or sodiumbenzophenone ketyl just prior to use.

Fisher reagent grade tetrahydrofuran (THF), benzene, and 1,2-dimethoxyethane (DME) were dried over $NaAlH_4$ and distilled under nitrogen just prior to use.

Fisher reagent grade hexamethylphosphorictriamide (HMPA) was dried over sodium and distilled under vacuum just prior to use.

Ketones

Eastman highest purity 2-methylbenzophenone (2-MBP), bp. 125-127°C/0.3 mm (lit.[8] bp. 134-137/2 mm) and benzophenone, mp. 48-49.5°C (lit.[9] mp. 48.1°C) were distilled under vacuum.

Fisher Certified A.C.S. grade acetone was dried over $MgSO_4$, then filtered, distilled and stored over 4Å molecular sieves, bp. 56°C (lit.[10] bp. 56.3°C).

Finton 4-tert-butylcyclohexanone was sublimed under nitrogen, mp. 43-48°C (lit.[11] mp. 49-50°C).

Eastman highest purity 9-fluorenone, mp. 82-85°C (lit.[12] mp. 85°C) Aldrich highest purity 2,4-dimethylbenzophenone, bp. 180-181°C/

5 mm (lit[13] bp. 178-181°C/12 mm); and Aldrich highest purity 2,5-dimethylbenzophenone, (lit[14] bp. 193-196°C/20 mm) were used without further purification.

Trans-2,2,6,6-tetramethylhept-4-ene-3-one ("trans enone") was obtained from a preparation by J. Ronald Boone, a coworker, and was also prepared as previously described.[54] It was shown to be greater than 99% pure by glc analysis.

Solutions of these ketones were stored in a glove box and shielded from light prior to use.

Alkyl Halides

Methyl bromide (Matheson 99.5% purity) was dried and purified by passing through a 30 cm tube of NaOH pellets and then through a 70 cm tube of Linde 4A molecular sieve. Fisher reagent grade bromobenzene, bp. 156°C (lit.[15] bp. 155-156°C); tert-butyl chloride, bp. 51-52°C (lit.[16] bp. 51.0°C); allyl bromide, bp. 70-71°C (lit.[17] bp. 71.3°C); and pivaloyl chloride, bp. 105-106°C (lit.[18] bp 105-106°C) were distilled through an 18 inch glass helix packed column.

Transition Metals

$CoCl_3$, CuCl, $CrCl_3$, $FeCl_2$, and $FeCl_3$ (Fisher sublimed) and the transition metal acetylacetonates (ROC/RIC) were opened only in the glove box, and used without further purification.

Organometallic Compounds

Grignard reagent solutions were prepared as previously described[3] from the following grades of magnesium metal: Baker Grignard grade turnings, Ventron chips (Lot 071173), ROC/RIC crystals, Dow No. 5, Dow doubly sublimed and Dow triply sublimed. The latter three grades of

magnesium were milled with a carbide tool prior to use. The former three grades were used without further milling. Grignard reagents were analyzed by hydrolyzing an aliquot with distilled water, adding excess standard H_2SO_4 and back titrating with standard NaOH to a phenolphthalein end point. Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10 using Eriochrome-Black T as an indicator. In some cases halide was determined by titration with $AgNO_3$ and back titration by KCNS with ferric alum indicator. In some cases the amount of active C-Mg was determiend by titrating active Grignard reagent with dry 2-butanol in xylene using 2,2'-biquinoline as an indicator. In those cases where all four types of analysis were carried out, the ratio Halide:C-Mg:Mg:Total Base was within 3% of 1.0:1.0:1.0:1.0.

Girgnard reagents in HMPA and THF were prepared by removing the ether from the Grignard reagent under vacuum and adding the appropriate solvent. Grignard reagents in HMPA were used within one week of preparation.

Lithcoa tert-butyllithium was analyzed by standard Gilman double titration method. Methyllithium was obtained from a preparation by John Watkins, a coworker, and analyzed by the Gilman double titration method. Solutions of $LiCuMe_2$, $LiCu_2Me_3$, ($Li_2CuMe_3 \rightleftarrows L_iCuMe_2 + MeLi$), and $LiCu(t\text{-}Bu)_2$ were also obtained from preparations by John Watkins and were stored at -78°C prior to use.

$LiAlH_4$ (Alfa Inorganic) and $LiAlD_4$ (Merck, Sharp and Dohme) were suspended in refluxing ether for 24 hours, then filtered. The clear solutions were standardized by standard aluminum analysis (EDTA

titration) prior to use.

Others

Authentic samples of 3-methyl-cis-2,2,6,6-tetramethylhept-4-ene-3-ol, 3-methyl-trans-2,2,6,6-tetramethylhept-4-ene-3-ol and 5-methyl-2,2,6,6-tetrametyl-3-heptanone were obtained from Paul Weeks, a postdoctoral assistant in the research group of Dr. H. O. House. Authentic samples of cis and trans-2,2,6,6-tetramethylhept-4-ene-3-ol were obtained from J. Ronald Boone, a coworker.

Aldrich (99%) 4-tert-butylbenzoic acid, mp. 165-167°C, (lit.[19] mp. 165-166°C); Aldrich (97%) 2,6-dimethylbenzoic acid, mp. 114-116°C (lit.[20] mp. 115.8-116.2°C); and Eastman highest purity p-dinitrobenzene (p-DNB) mp. 172-174°C (lit.[21] 172°C) were used without further purification.

Preparations

Miscellaneous

The preparations of 1-(2-methylphenyl)-1-phenylethylene and 1-(2-methylphenyl)-1-phenyl ethanol were carried out as previously described.[22] The preparation of active magnesium hydride has been previously described.[23] The preparation of acetone pinacol has been previously described.[24]

2,2-Dimethyl-1,1-diphenyl propanol

To a rapidly stirred solution of 0.375 mole "PhMgBr" in 300 ml of ether, was added 18.5 ml (0.15 mole) Pivaloyl chloride over a period of 60 minutes. The solution was stirred 24 hours and hydrolyzed with 10% H_2SO_4. The desired product distilled at 116-125°C/0.5 mm

(lit.[25] bp. 160-162°/5 mm). NMR: ($CDCl_3$, TMS) 10 H multiplet at 7.2 to 7.7δ, 1 H singlet at 2.28δ, 9 H singlet at 1.15δ. Single peak by glc on 2 foot 10% carbowax 20 M column and mass spectrum consistent with structure. M^+ weak (240), $M-H_2O$ (222), $M-H_2O$ and methyl (207) and M-tert-butyl (183) are characteristic.

4-tert-Butylbenzophenone

To a rapidly stirring solution of 0.040 mole p-tert-butylbenzoic acid in 200 ml ether was added 0.080 mole of "PhMgBr" in 64.0 ml of ether. The solution was allowed to stir overnight and was hydrolyzed with 10% H_2SO_4. After drying and stripping off the ether the crude product showed 1 peak by glc analysis. After distillation (bp. 100-112/0.5 mm, lit.[26] bp. 205/15 mm), NMR: ($CDCl_3$, TMS) 9 H multiplet at 7.2 to 7.7δ, 9 H singlet at 1.38δ. Mass spectrum was consistent with structure. M^+ = 238.

2-Methylbenzhydrol

Thirty mmoles (5.88 gms) of 2-methylbenzophenone was reduced with 15 mmoles of $LiAlH_4$ in THF/Et_2O at 0°. After 3.5 hours at room temperature, the reaction was hydrolyzed with aqueous NH_4Cl and dilute HCl. The ether layer was washed with aqueous $NaHCO_3$, dried with $MgSO_4$ and the ether removed under vacuum. The crude solid was recrystallized from hexane, mp 89.5-90.5 (lit.[27] mp. 89°C), IR: (neat between plates), 3.1μ (broad), 3.2-3.4μ (multiplet), 6.25μ, 6.3μ, 6.7μ, 6.85μ, 6.9μ. NMR ($CDCl_3$, TMS), 3 H singlet at 2.26δ, broad 1 H singlet at 2.25δ, 1 H singlet at 6.05δ, 9 H multiplet at 7.12-7.73δ.

2,2'-Dimethylbenzopinacol

Twelve mmole methylmagnesium bromide containing 2 mole % $FeCl_3$ was added to 10 mmole of 2-methylbenzophenone in 20 ml of diethyl ether. After 2.5 hours the reaction was hydrolyzed with aqueous NH_4Cl, the ether layer was dried with $MgSO_4$ and the ether was removed under vacuum. The crude product was recrystallized from $CHCl_3$ at 0°, washed with pet ether and air dried, mp 151-153°C (lit.[28] mp. 156°C), NMR ($CDCl_3$, TMS) 6 H singlet at 1.98δ, 2 H singlet (sharp) at 3.16δ, 16 H multiplet at 6.60-7.42δ, 2 H multiplet at 7.90-8.16δ.

CH_3CD_2OH

n-Butylacetate (142 g, 1.22 moles) in 100 ml of diethyl ether was reduced by slowly adding 0.65 mole of $LiAlD_4$ in 900 ml of diethyl ether. After addition of $LiAlD_4$ solution was complete, the reaction mixture was allowed to reflux for 2.5 hours, then slowly hydrolyzed with 200 ml of distilled water. The ether layer was decanted, dried over anhydrous $MgSO_4$ and filtered. The ether was removed by distillation through a two foot packed column. This procedure was repeated and the batches were combined. Fractional distillation yielded 94.1 g, (1.96 moles) CH_3CD_2OH.

CH_3CD_2Br

One mole of CH_3CD_2OH was added dropwise at 0° to a 500 ml round bottom flask containing 200 g of 48% HBr and 30 ml concentrated H_2SO_4. After all CH_3CD_2OH had been added, 51 ml of concentrated H_2SO_4 was added dropwise at room temperature. The reaction mixture was heated on an oil bath and the fraction boiling at 35-38° was collected. The

CH_3CD_2Br was washed with 10% Na_2CO_3 and dried over $MgSO_4$ (yield 96.3 g, 0.868 mole).

CH_3CD_2ONa

CH_3CH_2OH (0.96 mole) in 50 ml dimethoxyethane was added dropwise at 0° to 49.8 g (1.18 moles) NaH in 400 ml of dry dimethoxyethane with vigorous stirring. After addition of CH_3CD_2OH was complete, the reaction mixture was stirred for 19 hours at room temperature.

$(CH_3CD_2)_2O$

To the CH_3CD_2ONa, 0.8 mole of CH_3CD_2Br in 60 ml of dimethoxyethane was added slowly. The reaction mixture was stirred at room temperature for 17 hours, followed by heating to 40° for 7 hours, followed by stirring at room temperature overnight. The $(CH_3CD_2)_2O$ (22.5 g) was isolated by fractional distillation (bp 34.5-35.5). NMR analysis (singlet at 1.17δ) indicated the $(CH_3CD_2)_2O$ to be essentially 100% isotopically pure.

2,2,3,3-Tetramethylpropanol

To 0.40 mole of t-BuLi in 241 ml of hexane, 23 ml (0.33 moles) in 100 ml hexane was added slowly. After 4 hours the reaction was hydrolyzed. The organic layer was dried and roto-vapped to a viscous liquid. Recrystallization from ether gave a solid, mp 76-79°C (lit.[29] mp 80°C, hydrate) NMR ($CDCl_3$, TMS) 3 H singlet at 0.93δ, 2 H singlet at 1.18δ, 1 proton broad singlet at 1.53δ.

cis-2,2,6,6-Tetramethylhept-4-ene-3-one ("cis-Enone")

A solution of 11.19 gms (66.6 mmoles) of "trans-enone" in 250 ml hexane was photolyzed for 2 hours with a high intensity lamp using a

quartz filter. The solution (∿44% cis) was cooled to -78°C for 2 hours, then filtered. The solid ("trans-enone") was recycled for further photolysis. The hexane was pumped off and the mixture (∿77% cis) was further purified by preparative glc. The product obtained was generally > 99% pure by glc. Upon standing the "cis-enone" slowly isomerizes so fresh batches were prepared regularly. NMR ($CDCl_3$, TMS) 18 H singlet at 1.12δ, 2 H vinylic ab multiplet centered on 5.97δ (J_{ab} = 12 Hz).

3-tert-Butyl-trans-2,2,6,6-tetramethylhept-4-ene-3-ol

To 5.0 mmoles of "trans-enone" in 12.5 ml of ether at -78°C was added 7.0 mmoles of t-BuLi in 3.5 ml of hexane. The mixture was swirled until the "enone" went back into solution and was then reacted at -25°C for 7 hours. After hydrolysis with saturated NH_4Cl/H_2O, glc showed a mixture which was subsequently separated and identified by preparative glc, NMR, and mass spectroscopy. The products were: 1,2-reduction, trans-1,2-addition, and 1,4-addition. The latter two products predominated. (They have retention times close enough together to make preparative glc difficult, but the ketone can be moved away by further reaction of the mixture with "allylmagnesium bromide".) The trans-1,2-addition product was characterized: NMR($CDCl_3$, TMS) 27 H singlet at 1.03δ, 1 H broad singlet at 1.57δ, 2 H vinylic ab pattern centered on 5.60δ (J_{ab} ∿ 16); IR (neat, film) peaks at 3610 cm^{-1} (-O-H), 3010 cm^{-1} (=C-H), 2960 cm^{-1} (-C-H), 1692 (C=C), 1477 cm^{-1}, 1390 cm^{-1}, 1365 cm^{-1} (C-H and $-CH_3$ bending), 972 cm^{-1} (trans CH=CH); mass spectrum, weak molecular in peak at m/e 226, (M-1) peak at

m/e 225, and abundant fragments at m/e 169, 154, 111, 95, 83, 69, 57, 55, 43, 41, and 29, metastable at m/e 135; bp 61-63°C/0.2 mm; n_D^{25} 1.4583; Analysis, Calculated for $C_{15}H_{30}O$: C, 79.58%; H, 13.36%. Found: C, 79.56%; H, 13.34%.[30]

3-tert-Butyl-cis-2,2,6,6-tetramethylhept-4-ene-3-ol

To 5.0 mmoles "cis-enone" in 12.5 ml of ether at -78°C was added 7.0 mmoles of t-BuLi in 3.5 ml of hexane. The mixture was reacted for 7 hours at -25°C, then hydrolyzed with saturated NH_4Cl/H_2O. Glc of the crude product showed a mixture which was subsequently separated and identified by preparative glc, NMR, and mass spectroscopy. The products were: 1,2-reduction, trans-1,2-addition, 1,4-addition and cis-1,2-addition. The latter product predominated. The cis-1,2-addition product was characterized: NMR ($CDCl_3$, TMS) 18 H singlet at 1.08δ, 9 H singlet at 1.18δ, 1 H broad singlet at 1.67δ, 2 H vinylic pattern at 5.38δ; IR (neat, film) peaks at 3635 cm^{-1} (-O-H), 3010 cm^{-1} (=C-H), 2960 cm^{-1} (-C-H), 1665 cm^{-1} (C=C), 1482 cm^{-1}, 1373 cm^{-1} (-C-H and $-CH_3$ bending), 725 cm^{-1} (cis CH=CH); mass spectrum, weak molecular ion peak at m/e 226, (M-1) peak at m/e 225, and abundant fragments at m/e 169, 151, 111, 95, 83, 69, 58, 57, 55, 43, 41, and 28, metastable at m/e 135; bp ∿ 74°C/0.2 mm; n_D^{25} 1.4701; Analysis, Calculated for $C_{15}H_{30}O$: C, 79.58%; H, 13.36%. Found: C, 79.73%, H, 13.27%.[30]

5-tert-Butyl-2,2,6,6-tetramethyl-3-heptanone

To 10.0 mmoles of $LiCu(t\text{-}Bu)_2$ in 5 ml hexane, 2.5 ml ether and 35 ml DMS at -78°C, was added 5.0 mmoles of "trans-enone" in 12.5 ml ether. The mixture was reacted at -55°C for 2 hours, stored at -78°C for 16

hours, then placed in a -55°C bath which was allowed to slowly warm to room temperature (3 hours). After hydrolysis (with saturated NH_4Cl/H_2O), the layers were separated and the ether was removed. Glc of the crude product showed a mixture which was subsequently separated and identified by preparative glc, NMR, and mass spectroscopy. The products were: 1,2-reduction, 1,2-addition, dimer (probably at the 5-position), and 1,4-addition. The latter product predominated. The 1,4-addition product was characterized; NMR ($CDCl_3$, TMS) 18 H singlet at 0.95δ, 9 H singlet at 1.18δ, 1 H multiplet at 2.17δ, 2 H doublet at 2.48δ; IR (neat, film) peaks at 2965 cm^{-1}, 1482 cm^{-1}, 1370 cm^{-1} (various C-H vibrations) and 1714 cm^{-1} (C=O); mass spectrum, molecular ion peak at m/e 226 with abundant fragments at m/e 169, 113, 85, 71, 57, 43, 41, and 29; bp 57-59°C/0.1 mm; n_D^{25} 1.5409; Analysis, Calculated for $C_{15}H_{30}O$: C, 79.58% H, 13.36%. Found: C, 79.53%; H, 13.37%.[30]

3-Allyl-cis-2,2,6,6-tetramethylhept-4-ene-3-ol

To 2.9 mmoles of "cis-enone" in 36 ml ether was added 12.0 mmoles of "Allymagnesium bromide" in 14 ml of ether. After 6 hours the reaction was hydrolyzed with NH_4Cl/H_2O. The ether was dried and removed. Glc of the crude reaction mixture showed it to be approximately 2% trans-1,2-addition, 1% 1,2-reduction, and 97% cis-1,2-addition. The cis-1,2-addition product was purified by preparative glc and characterized: NMR ($CDCl_3$, TMS) 9 H singlet at 0.98δ, 9 H singlet at 1.12δ, 1 H broad singlet at 1.68δ, 2 H multiplet at 2.27δ, 2 H vinylic ab pattern ($J_{ab} \sim 7$ Hz) centered on 5.12δ with an overlapping 3 H vinylic pattern centered on 5.0δ; IR (neat, film) peaks at 3570 cm^{-1} (-O-H), 3080 cm^{-1}, 3010 cm^{-1} (=C-H), 2960 cm^{-1} (-C-H), 1640 cm^{-1} (C=C), 1475 cm^{-1}, 1385 cm^{-1}, 1363

cm^{-1} (-C-H and $-CH_3$ bending), 997 cm^{-1}, 912 cm^{-1} ($-CH=CH_2$), 754 cm^{-1} (cis CH=CH); mass spectrum, very weak molecular ion peak at m/e 210 as well as weak peaks at m/e 195, 192, and 177 corresponding to loss of CH_3, H_2O, and both. Abundant fragments at m/e 169, 153, 83, 69, 57, 55, 43, 41, 29; bp 68-70°C/0.15 mm; n_D^{25} 1.4645; Analysis, Calculated for $C_{14}H_{26}O$: C, 79.94%; H, 12.46%. Found: C, 79.85%; H, 12.48%.[30]

3-Allyl-trans-2,2,6,6-tetramethylhept-4-ene-3-ol

To 33.0 mmoles of "trans-enone" in 250 ml ether was added 86.0 mmoles of "Allylmagnesium bromide" in 100 ml ether. After 10 hours the reaction was hydrolyzed with NH_4Cl/H_2O. The ether was dried and removed. Glc of the crude mixture showed it to be approximately 2% 1,2-reduction and 98% trans-1,2-addition. The trans-1,2-addition product was purified by preparative glc and characterized: NMR ($CDCl_3$, TMS) 9 H singlet at 0.90δ, 9 H singlet at 1.05δ, 1 H broad singlet at 1.58δ, 2 H multiplet at 2.33δ, 2 H vinylic ab pattern ($J_{ab} \sim 12.5$ Hz) centered on 5.47δ with an overlapping 3 H vinylic pattern centered on 5.0δ; IR (neat, film) peaks at 3575 cm^{-1} (-OH), 3081 cm^{-1}, 3025 cm^{-1} (=C-H), 2968 cm^{-1} (-C-H), 1642 cm^{-1} (C=C), 1480 cm^{-1}, 1395 cm^{-1}, (-C-H and $-CH_3$ bending), 1012 cm^{-1}, 925 cm^{-1} ($-CH=CH_2$), 990 cm^{-1} (trans CH=CH); mass spectrum, very weak molecular ion peak at m/e 210 as well as weak peaks at m/e 169, 153, 111, 83, 69, 57, 55, 43, 41, and 29; bp 54-56°C/0.2 mm; n_D^{25} 1.4514; Analysis, Calculated for $C_{14}H_{26}O$: C, 79.94%; H, 12.46%. Found: C, 79.82%; H, 12.44%.[30]

1-(2,4-Dimethylphenyl)-1-phenylethanol

To a solution of 0.325 gms (1.55 mmoles) of 2,4-dimethylbenzophenone in 10 ml ether was added 2.85 mmole of "CH_3MgBr" in 2.6 ml of

ether. After 7 hours the reaction was hydrolyzed with saturated NH_4Cl/H_2O. The mixture was dried and the ether was removed. The product was shown to be greater than 95% pure by NMR spectroscopy. NMR: ($CDCl_3$, TMS) 8 H multiplet at 6.8 to 7.7δ; 3 H singlet at 1.83δ; 3 H singlet at 1.93δ; 3 H singlet at 2.28δ; 1 H singlet at 2.20δ.

1-(2,5-Dimethylphenyl)-1-phenylethanol

To a solution of 0.0543 gms (0.259 mmole) of 2,5-dimethylbenzophenone in 10 ml ether was added 0.465 mmole of "CH_3MgBr" in 0.20 ml ether. After 4 hours, the reaction was hydrolyzed with saturated NH_4Cl/H_2O. The mixture was dried and the ether removed. The product was shown to be greater than 95% pure by NMR spectroscopy. NMR: ($CDCl_3$, TMS) 8 H multiplet at 7.0 to 7.6δ; two 3 H singlets close together at 1.88 and 1.90δ; 3 H singlet at 2.38δ; 1 H broad singlet at 2.17δ.

2,6-Dimethylacetophenone

To a solution of 2.02 gms (135 mmoles) 2,6-dimethybenzoic acid in 50 ml ether at -60°C was added 1 equivalent (15.62 ml; 0.95 M) MeLi in ether. After allowing the solution to warm to -40°C, a second equivalent of MeLi was added. The solution was allowed to warm to room temperature and stir for 12 hours. A very poor yield of a mixture of ketone and alcohol was obtained after hydrolysis as well as recovery of most of the starting acid. This crude mixture was used as obtained to make the next product.

1-(2,6-Dimethylphenyl)-1-phenylethanol

To a solution of the crude product in the above preparation in 20 ml ether, was added 10.0 mmoles of "PhMgBr" in ether. The reaction was allowed to stir 12 hours at room temperature. After hydrolysis a mixture was obtained. Preparative glc on a 2 foot 10% Carbowax 20 M column gave a sample which was consistant with 1-(2,6-dimethylphenyl)-1-phenylethanol by NMR and mass spectroscopy. Mass spectrum: M^+ = 226, M-H_2O (208), M-(H_2O + Me)(193) M-(H_2O and 2 Me's)(178) are characteristic. NMR: ($CDCl_3$, TMS) 3 H singlet at 1.23δ; 3 H singlet at 1.35δ; 3 H singlet at 2.33δ; 8 H multiplet at 7.2-7.9δ (1 H singlet (OH) not found). Upon heating this alcohol eliminates to form the olefin NMR: ($CDCl_3$, TMS) 3 H singlet at 1.17δ; 3 H singlet at 2.08δ; 2 H vinyl multiplet centered on 5.50δ, 8 H multiplet at 7.1 to 7.4δ.

Methods

Apparatus and Procedure

A Varian A-60D, 60 MHz spectrometer was used for recording nuclear magnetic resonance spectra. GLPC analyses were carried out on F and M Models 700 and 720 gas chromatographs. Materials used in this study were transferred in a glove box described elesewhere[31] or in Schlenk tubes under a blanket of nitrogen.

Calibrated syringes equipped with stainless steel needles used for transfer of reagents. Ketone and metal salt solutions were prepared by weighing the reagent in a tared volumetric flask, and diluting with the appropriate solvent. All metal solutions were used within 24 hours of preparation. In cases where the metal salt was not ether soluble, a

weighed mass was added directly to the Grignard solution immediately prior to the addition of the ketone. The solution of "CH_3MgBr" + active MgH_2[32] was prepared by placing 10 ml of 0.25 M MgH_2 is a 250 ml flask under N_2 flush and adding 50.42 ml of 2.38 M "CH_3MgBr" (prepared from ROC/RIC magnesium, 120 mmoles).

Reactions in General

Glassware and syringes were flamed and taken into a glove box under vacuum. The appropriate amounts of solvent and Grignard reagent solutions were syringed into a septum capped flask. An appropriate amount of ketone solution was added with swirling. (In some cases the inverse of this addition procedure was used). In those cases in which the reaction was carried out in the presence of a transition metal salt, the salt was added immediately prior to addition of ketone. When low temperatures were required, a capped flask was removed from the dry box and immersed in a bath at the appropriate temperature before addition of the ketone. After complete reaction the mixture was hydrolyzed with saturated aqueous NH_4Cl solution under a nitrogen atmosphere. The ether layer was separated, dried over anhydrous $MgSO_4$ and filtered. The solvent was then removed under vacuum.

The low Grignard to benzophenone ratio reactions typically involved addition of 0.625 mmole of ketone to 0.9 mmole of Grignard reagent in a total volume of 5 ml of ether. The high Grignard to benzophenone ratio reactions generally involved addition of 0.3 mmole of ketone to 120 mmole of Grignard reagent in a total volume of 80 ml of ether. Reactions were usually allowed to proceed for 4 hours before hydrolysis.

The Grignard reactions with acetone were generally carried out by mixing 0.28 mmole of Grignard with 0.19 mmole of acetone in 1.5 ml of ether and were usually allowed to proceed for 20 minutes before hydrolysis with 50-100 Ml saturated NH_4Cl/H_2O. These solutions were dried over $MgSO_4$ before glc analysis.

The Grignard reactions with "cis-and trans-enone" were carried out similarly except that 0.10 mmole of "enone" was generally reacted with 0.05 mmole of organometallic compound in 1.5 ml of ether. The rate studies utilized 0.05 mmole of "enone" and 0.05 mmole "CH_3MgBr" in 2.0 ml ether.

The identification of all products from the reaction of "CH_3MgBr" with benzophenone and 2-MBP was determined by NMR analysis employing $CDCl_3$ as a solvent with internal TMS. For the products arising from reaction with benzophenone: 1,2-addition was determined by the observation of the methyl group attached to the carbonyl carbon (1.92δ), benzopinacol was determined by the -OH hydrogen (3.05δ), and benzhydrol was determined by the hydrogen attached to the carbonyl carbon (5.80δ). For the products arising from reaction with 2-MBP: 1,2-addition was determined by observation of the methyl group attached to the carbonyl carbon (1.85δ) and the methyl group bound to the ring (1.96δ), 2,2'-dimethylbenzopinacol was determined by observation of the -OH hydrogen (3.16δ) and the methyl group bound to the ring (2.26δ). 2,2,3,3-Tetramethylbutane (singlet 0.88δ) was employed as an internal standard.

The identification of all products from the reaction of "tert-butylmagnesiumchloride" ("t-BuMgCl") with benzophenone and 2-MBP was

by NMR[33] under nitrogen analysis employing $CDCl_3$ as a solvent with internal TMS. For products arising from reaction with benzophenone: 1,2-addition was determined by the observation of the tert-butyl group attached to the carbonyl carbon (1.15δ), 1,6-addition by the tert-butyl group on the ring (0.93δ) and air oxidation of the 1,6-addition product by the tert-butyl group on the ring (1.38δ). Generally air oxidation was avoided in the workup procedure, but it was shown to be a quantitative conversion, and when it does occur, the proper analysis is obtained from the total of the two, 1,6-addition peaks. For the products arising from reaction with 2-MBP: 1,2 addition was determined by the tert-butyl group attached to the carbonyl carbon (0.98δ), 1,6-addition by the tert-butyl group on the ring (0.87δ), and oxidized 1,6-addition by the tert-butyl group on the ring (1.18δ). Generally, diphenyl methane was employed as internal standard (10 H, 7.22δ; 2 H, 4.00δ). Occasionally, nitromethane (4.32δ) or acetone (2.13δ) was employed.

The identification of products of Grignard reactions with fluorenone was made by comparison of NMR to the NMR of equivalent products in the benzophenone reactions. The structure of the ketones is very similar and the similarity in the results of the study did not seem to warrant synthesis of authentic samples. Product analysis was determined based on the following assignments: methyl-1,2-addition by the methyl group on the carbonyl carbon (1.68δ), tert-butyl-1,2-addition by the tert-butyl group on the carbonyl carbon (1.25δ), tert-butyl-1,6-addition by the tert-butyl group on the ring (0.97δ), oxidized

tert-butyl-1,6-addition by the tert-butyl group on the ring (1.35δ) and pinacol by the -OH hydrogens (3.23δ). The same internal standards were used as with benzophenone.

The identification of all products from the reaction of Grignard reagents with acetone was determined by glc on a 12 foot, 20% Carbowax 20 M column programmed between 60 and 180°C (60° for 14 minutes, 130° for 14 minutes, 180° for 14 minutes). Injection port temperature: 220°C, detector temperature: 300°C and helium flow rate: 60ml/minute were employed. Retention times varied slightly with conditions, but typically they were: acetone, 7.0 minutes, tert-butyl alcohol, 10.1 minutes, iso-propyl alcohol, 12.5 minutes, 1,1,2,2-tetramethylpropanol, 19.6 minutes, dodecane, 23.5 minutes, and pinacol, 36.0 minutes. Dodecane was employed as internal standard and relative response factors were determined regularly.

The identification of all the products from the reactions with "cis- and trans-enones" was determined by glc on a 12 foot, 20% Carbowax 20 M column at 125°C. Injection port temperature: 180°C, detector temperature: 240°C and helium flow rate: 80ml/minute were generally utilized. Retention times varied with conditions, but typically were: dodecane, 10.3 minutes, "cis-enone", 12.6 minutes, "trans-enone", 14.9 minutes, methyl-1,4-addition, 17.4 minutes, methyl-trans-1,2-addition, 19.7 minutes, cis- and trans-1,2-reduction, 24.8 minutes, allyl-trans-1,2-addition, 34.0 minutes, allyl-cis-1,2-addition, 50.8 minutes, tert-butyl-trans-1,2-addition, 38.9 minutes, tert-butyl-1,4-addition, 42.9 minutes, tert-butyl-cis-1,2-addition, 68.6 minutes. Dodecane was

employed as internal standard and relative response factors were determined regularly. In some cases cis- and trans-1,2-reduction products were separated on a 12 foot 10% TCEP column at 115°C, but generally they were analyzed together and identified as "1,2-reduction products".

In general, reactions involving low Grignard to ketone ratios had essentially 100% material balances. Those reactions involving high Grignard to ketone rations gave somewhat low material balances (ca. 80%). This is probably due to products being physically removed from the reaction vessel by the large amount of methane produced on hydrolysis. Addition of a dry-ice acetone condensor to the flask prior to hydrolysis improved material balances to nearly 100%.

"CH_3MgBr" + 2-MBP, Low Temperature Product Versus Time Studies[34]

The Grignard reactions were run in a special kinetics flask which consisted of a 100 ml round bottomed flask fitted with a septum cap and placed in a dry-ice acetone bath in order to control the reaction temperature. A two-way teflon stopcock was attached near the bottom of the flask (through the back) at such an angle as to allow magnetic stirring. When a sample was desired, the flask was pressurized with nitrogen and the stopcock opened briefly to allow the appropriate amount of sample to be forced into a saturated aqueous NH_4Cl solution cooled to 0° (vigorously stirred). A fast flush of nitrogen was directed along the stopcock delivery tube to further reduce any contact with the air prior to hydrolysis. The hydrolyzed aliquots were worked up and analyzed in the usual fashion.

Reactions in Deuterated Ethers

The reaction using "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ and allowed to react with ketone in $(CH_3CD)_2O$ was carried out in the usual fashion. For the reaction using "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ and allowed to react with the ketone in $(CH_3CD_2)_2O$, a special procedure was employed. Eighty mmoles of "CH_3MgBr" (prepared from excess Dow doubly sublimed magnesium in $(CH_3CH_2)_2O$) was syringed under N_2 flush into a 200 ml round bottomed flask via a 3-way stopcock. The flask was evacuated, placed in an oil bath at 100° for 4 hours, then allowed to cool at room temperature. It was then refilled with N_2. Twenty milliliters of $(CH_3CD_2)_2O$ was syringed into the flask under N_2 flush and the solution stirred until all of the Grignard reagent had dissolved. The reaction with ketone was then carried out as usual.

Reactions Showing the Selectivity of the Magnesium Hydride Reducing Species[35]

To an ether solution containing 120 mmoles of "CH_3MgBr" or "CH_3MgBr" + "MgH_2"[32] was added 0.3 mmole of 2-methylbenzophenone and 0.3 mmole of acetone. Reactions were carried out for 4 hours and hydrolysis was followed by vacuum stripping of the volatile portion. Analysis of this portion was obtained by GLPC on a 19 foot, 15% Diglycerol on 60/80 mesh Chromasorb W column at 60° and a flow rate of 60 ml/min of helium using 3,3,5-trimethylcyclohexanone as an internal standard. The retention times for the t-butanol (addition product) and the i-propanol (reduction product) were 12 and 15 minutes respectively. Extraction of the residue after vacuum stripping gave the rest of the reaction products which were then analyzed in the normal manner.

Reaction Showing the Stereochemistry of Reduction of 4-t-Butylcyclohexanone by the Magnesium Hydride Species[35]

These reactions were carried out in the normal manner. Analysis was carried out by GLPC using 10% FFAP on Diatoport S on a 20 foot column at 150° with a flow rate of 20 ml/min of helium using 3,3,5-trimethylcyclohexanone as the internal standard. The retention times are as follows: axial alcohol, 39.5 minutes and equatorial alcohol 47 minutes; and the addition products: axial alcohol, 20 minutes and equatorial alcohol, 34 minutes. All retention times were determined by comparison to authentic compounds.

Formation, Separation and Identification of Threo and Erythro 2,2'-Dimethylbenzopinacol[34]

A mixture (roughly 50:50) of the two pinacols was prepared by reacting 25 mmoles CH_3MgBr with 5.0 moles 2-MBP and 0.125 mole (0.5 mole %) $FeCl_3$ at -30°. After 4 hours, the reaction was hydrolyzed with aqueous NH_4Cl at -30°. Normal workup followed by washing the crude solid with pet ether gave a mixture of the two pinacols.

The two pinacols were separated by column chromatography on silica gel, eluting first with 10% CH_2Cl_2 in pet ether. The "normal" thermodynamic pinacol washed off the column first, followed closely by the kinetic one (i.e., the one formed only at low temperature).

The kinetic pinacol was identified by comparison of its spectra with the already known thermodynamic form. Mass spectra: both gave identical spectra with no significant peaks above 195. Both are very similar to that of a mixture of 2-MBP and 2-methylbenzhydrol.

NMR: ($CDCl_3$, TMS) Thermodynamic; 6 H singlet 1.98δ, 2 H

multiplet 7.90-8.16δ. Kinetic: 6 H singlet 1.82δ, 2 H singlet (broad) 3.23δ, 18 H multiplet 6.84-7.66δ, IR: Thermodynamic 2.80μ(broad), 3.25-3.44μ. Kinetic: 2.78μ (broad), 3.27μ and 3.37μ, fingerprint region very similar to the other pinacol.

		λ_{max}	E
UV:	Thermodynamic	225	1200
	Kinetic	254	1400

Essentially identical spectra - slightly different vibrational fine structure.

$Pb(OAc)_4$ Oxidation of Threo and Erythro 2,2'-Dimethylbenzopinacol[34]

0.432 Mole 2,2'-dimethylbenzopinacol (55% thermodynamic, 45% kinetic) was allowed to react at room temperature with 0.158 mole $Pb(OAc)_4$ in 10 ml acetic acid for 3 days. After hydrolysis and normal workup, NMR analysis showed 34% kinetic, 55% thermodynamic and 11% ketone (30% complete reaction).

Study of the Threo/Erythro Pinacol Equilibrium at -25°C

These reactions were carried out as usual, except that the reagents were mixed at -78°C and then transferred to a bath at -25°C. Time zero was defined as time of transfer to -25°C bath. Hydrolysis was carried out as close to -25°C as possible. Individual reactions were carried out for each point determined in the study.

Formation, Separation and Identification of the "Other" in the 400/1 "CH_3MgBr" + 2-MBP Reactions

The reactions which contained "other" as a product were combined and a small amount of this product was obtained by preparative glc. NMR: ($CDCl_3$ TMS); 3 H singlet, 1.22δ; 3 H singlet, 1.34δ; 3 H singlet, 2.33δ; 1 H broad singlet, 1.58δ; 8 H multiplet 7.2-7.9δ. (Same as that of 1-(2,6-dimethyl phenyl)-1-phenylethanol).

IR: Indicates that the compound is an alcohol (broad band at 3500 cm^{-1}) and that it probably has one ring with no methyls (5 adjacent H's band at 703 cm^{-1} and 760 cm^{-1}) and another ring with two methyls (3 adjacent H's: band at 790 cm^{-1}). Mass spectrum: Indicates a ring with no methyl groups (m/e = 91, 77, 78 and 79) and a ring with two methyl groups (m/e = 105, 91, 92, 93). The lower m/e portion of this spectrum (below 178 = m/e) agrees well with that of 1-(2,6-dimethyl-phenyl)-1-phenylethanol, however, the higher m/e region does not. (Possibly due to impurities in the sample) Synthesis of the alcohols 1-(2,5-dimethylphenyl)-1-phenylethanol and 1-(2,4-dimethylphenyl)-1-phenylethanol showed their NMR spectra to be very different from that of the "other". It seems that two methyls in ortho positions are necessary to produce this distinctive NMR spectrum. While this evidence may not be completely unequivocal, it does strongly indicate the structure of the "other" product in these reactions to be 1-(2,6-dimethylphenyl)-1-phenylethanol.

CHAPTER III

RESULTS AND DISCUSSION

Initial Observations

When "CH_3MgBr" was allowed to react with 2-MBP in large Grignard: ketone ratios, the product distribution varied widely with both the grade of magnesium and the method of preparation of the Grignard reagent (Table 1). While the formation of 2-methylbenzhydrol appears to be dependent mainly on the method of preparation of the Grignard reagent, the amount of 2,2'-dimethylbenzopinacol produced appears to depend only on the grade of magnesium used. The "other"[36] product listed in the table also appears to depend only on the grade of magnesium.

The various grades of magnesium used in these experiments were analyzed by four different methods: Spark Source Mass Spectroscopy, Emission Spectroscopy, Proton Excited X-ray Spectroscopy, and X-ray Fluorescence Spectroscopy. These methods all gave similar results. Analysis by Spark Source Mass Spectroscopy of the transition metal impurities in the various grades of magnesium used in this study are given in Table 1. Multiple regression and correlation analysis[37] was carried out on this data. The relationship involving transition metal content in the magnesium metal and pinacol formation was shown to have a "correlation coefficient" of 0.905 and an "index of determination"[38] of 0.819. The "other" product was shown to have a "correlation

coefficient: of 0.967 and an "index of determination" of 0.935. Thus the relationship between the amount of transition metal present in the magnesium metal used to prepare the Grignard reagent and the amount of pinacol and "other" product formed is excellent. On the other hand, the hydrol formed did not correlate at all with the transition metal content of the magnesium. Because the formation of 2,2'-dimethylbenzopinacol and that of 2-methylbenzhydrol appear to be quite different in nature, they will be treated in separate sections.

Investigation of Magnesium Purity and Solvent Effects

Methylmagnesium bromide prepared by the reaction of single-crystal magnesium with excess CH_3Br (this method produces the purest Grignard[2,7b]) reacts with benzophenone (Grignard/ketone ratio $\sim$ 1.5) in diethyl ether to give more than 99.5% 1,2-addition, while the same reaction using a less "pure" Grignard reagent[2,7b] (prepared from Grignard Grade turnings employing excess magnesium) gave 98.0% 1,2-addition (Table 2). (In the former case no benzopinacol was detected by NMR within the limits of detection, whereas in the latter case 2% was observed). At higher G/K ratios, larger amounts of by-product were observed. (At G/K = 125,"CH_3MgBr"(GGT, excess Mg) gave only 90.6% 1,2-addition and 9.4% benzopinacol). There is obviously some impurity in the Grignard reagent prepared from Grignard Grade turnings whose effect is substantially increased as the G/K ratio is increased. Doping the ketone solution with $FeCl_3$ (4-40,000 ppm) followed by reaction with "CH_3MgBr"(SC, excess CH_3Br) gave by-product benzopinacol (1.0-70.5%) in amounts proportional to the amount of catalyst added. Since no

detectable by-product is formed in experiment 2, whereas $FeCl_3$ causes significant quantities of by-product to be formed (experiments 5-9), it appears that the presence of iron causes a considerable shift in the mechanism of the reaction.[39] Since "CH_3MgBr" (SC, excess CH_3Br) had been shown to react with benzophenone and 2-methylbenzophenone in a polar manner,[2,7b] and since benzopinacol may be expected to occur through some sort of SET intermediate, it appears that the reaction of "CH_3MgBr" with benzophenone in diethyl ether normally proceeds via a polar mechanism except when catalyzed by a transition metal compound, at which time a SET pathway becomes predominant.

Similar observations were made when the solvent was changed to THF. "CH_3MgBr"(SC, excess CH_3Br) reacted with benzophenone to give 99.2% 1,2-addition and only 0.8% of the ketone was converted to benzopinacol. On the other hand, when the benzophenone solution was doped with 4000 ppm $FeCl_3$, benzopinacol accounted for 72.0% of ketone and 1,2-addition for only 27.0% (the other 1.0% was benzhydrol.) As may have been expected, the more polar solvent (THF) better stabilizes the ketyl; therefore, more by-product was observed than in the equivalent experiment in diethyl ether. When the solvent is further changed to HMPA, it would appear that the reaction must proceed entirely by one mechanism (no competition between polar and SET) since doping with $FeCl_3$ does not significantly change the product ratio. However, further investigation along these lines shows that HMPA inactivates the iron catalyst (Table 4), hence, both reactions are probably proceeding by the same mechanism.

Holm and Crossland have clearly demonstrated that the reaction of "t-BuMgCl" (prepared from Dow sublimed magnesium in excess Mg) with

benzophenone proceeds predominantly, if not entirely, through a SET mechanism.[6] Since the purity of the magnesium was shown to be important with "CH_3MgBr", it was considered necessary to determine whether or not their findings were the result of a transition metal catalyzed reaction. We have found that the reaction of "t-BuMgCl" with benzophenone in diethyl ether gives from 48.0 to 50.0% conversion to 1,6-addition products, 38.2 to 42.3% conversion to 1,2-addition product, and 8.8 to 12.7% conversion to benzopinacol, regardless of the grade of Grignard reagent used, the ratio of G/K (if Grignard is in excess), or the presence of 400 ppm $FeCl_3$ (Table 3). This is sufficient indication that the reaction of "t-BuMgCl" with benzophenone in diethyl ether proceeds predominantly through a SET mechanism even in the most favorable case when the Grignard reagent was prepared from single crystal magnesium in excess t-C_4H_9Cl. Again, experiment 19 shows that in a reaction which is already proceeding predominantly through SET, the presence of a more polar compound in the ether (in this case the excess benzophenone) evidently stabilizes the ketyl radical anion and aids in escape from the solvent cage, forming a larger percentage of benzopinacol. In THF solvent, 41.3%, 1,6-addition product, 47.0% 1,2-addition product and 11.7% benzopinacol was formed. The same reaction in HMPA gave 26.0% 1,6-addition product, 72.3% 1,2-addition product, and 1.7% benzopinacol. No real information can be drawn from the iron doped experiment in HMPA. The doped experiment in THF (experiment 22) gives less 1,2-addition product than the undoped one (experiment 21). This trend is in the right direction to indicate a shift away from a polar mechanism,

but the magnitude of the change is too small to be significant and most likely the mechanism is SET in each case. The importance of the t-BuMgCl-Ph_2C=O reaction lies in the fact that in ether the product ratio does not depend on the "purity" of the magnesium used to prepare the Grignard reagent. It appears, then, that the reaction, when compared to the work of Holm and Crossland,[6] proceeds through a SET mechanism, even when the best grade of magnesium available is used to prepare the Grignard.

It appears from all these data that "CH_3MgBr" addition to benzophenone in ether solvent is proceeding predominantly, if not entirely, by a polar mechanism whereas the reaction of "t-BuMgCl" under the same conditions is proceeding by a SET pathway. It is clear that a reaction which normally would proceed by a polar mechanism can proceed by a SET pathway, if the magnesium used to prepare the Grignard reagent contains parts per million of transition metal impurities.

Mechanism of Pinacol Formation

Since the formation of pinacols in Grignard reactions with ketones is considered indicative of a SET pathway, the multiple regression and correlation analysis points to the existence of a transition metal catalyzed SET pathway in the reaction of "CH_3MgBr" with 2-MBP. Using $FeCl_3$ as a typical transition metal impurity, we have demonstrated that the relative amount of pinacol found in the reaction products depends on the concentration of iron in the Grignard reagent, (Table 2). These results lead to the conclusion that the formation of pinacol in the reaction of "CH_3MgBr" with benzophenone proceeds by a SET pathway and is

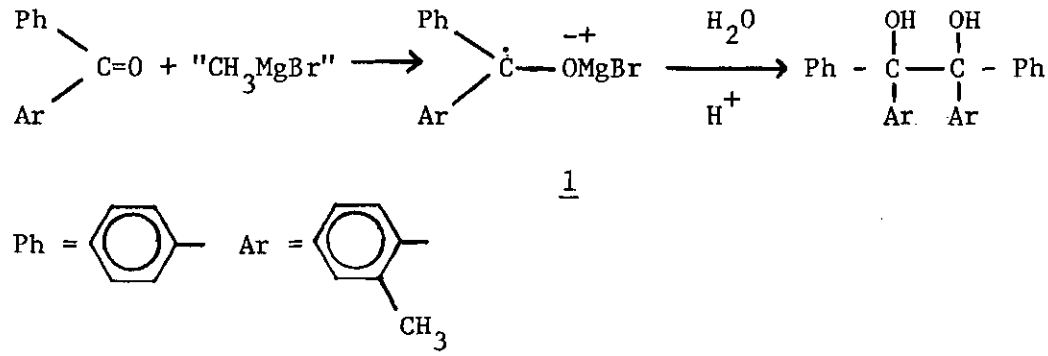
iron catalyzed.

Once the catalytic effect of iron had been determined, a general study of the effect of transition metal salts was conducted (by Jerry D. Buhler)[34] (Table 5). Only the first row transition metals from vanadium to nickel showed any catalytic behavior. Within this series the amount of pinacol formed increased from vanadium through iron then decreased again through nickel. It is interesting to note that for any given metal, the particular salt or oxidation state of that salt, does not seem to be important. Apparently the Grignard reagent is capable of reducing any of the transition metal ions to a common reactive state.[40]

In an effort to find a way to remove the by-product forming impurities in the Grignard reagent, various complexing agents were screened as by-product inhibitors (by Jerry Buhler).[34] In the reaction of 1.5 mmole of methylmagnesium bromide with 1.0 mmole of 2-MBP in the presence of 0.05 mole % $FeCl_3$, addition of 2.0 mole % of ethlenediaminetetraacetic acid-disodium salt, triphenylphosphine, 1,10-phenanthroline, 2,2'-biquinoline, tetramethylenediamine or hexamethylphosphoramide had no effect on the product distribution. In each case the product ratio was about 60% 1,2-addition and 40% 2,2'-dimethylbenzopinacol (including the reaction with no added complexing agent.)

In order to shed some light on the mechanism of pinacol formation, a study of the role of ketyls in the reaction of "CH_3MgBr" with 2-MBP was carried out (by Irene Lopp).[41] We were able to show by esr and uv spectroscopy that the bromomagnesium ketyl of 2-MBP (1) is the intermediate ketyl formed in the Grignard reaction, and that a direct

relationship exists between the amount



(1)

of ketyl observed during the reaction and the amount of 2-2'-dimethyl-benzopinacol found after hydrolysis.[42]

A low temperature study of the formation of products with respect to time was conducted (by Jerry D. Buhler)[34] for the iron catalyzed reaction of "CH_3MgBr" with 2-MBP (Table 6). Both addition product and pinacol appear in normal fashion and in constant ratio throughout the entire reaction, indicating either that they are coming about via the same pathway, or via competing pathways of similar kinetic order. (This rules out the possibility than an impurity in the Grignard reagent reacts with the ketone in a stoichiometric manner as will be shown to be the case in the formation of benzhydrol). A comparison of this reaction with the uncatalyzed reaction (parenthetical values, Table 6) shows that the 1,2-addition product was formed at about twice the rate in the catalyzed reaction as in the uncatalyzed reaction.[43] It appears possible, therefore, that some of the 1,2-addition product could be formed through a SET pathway, however since the catalyzed and uncatalyzed

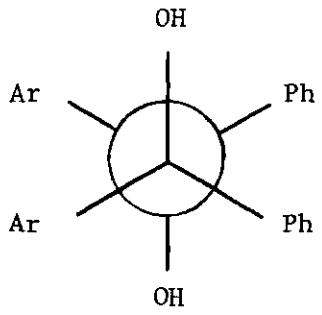
rates are so similar it does not at all appear clear that true catalysis is taking place. In addition, this result does not allow one to distinguish between the possibilities that both the catalyzed and uncatalyzed reactions producing 1,2-addition product proceed by a polar mechanism or both by a SET mechanism. It does not seem reasonable that the uncatalyzed reaction is proceeding by a polar mechanism and the catalyzed reaction by a SET mechanism since the rates of catalyzed and uncatalyzed reactions are so similar. By the use of probes in both the R-group of the Grignard reagent and the substrate, it appears possible that both the polar and SET mechanism are competing in this system.[44]

During this low temperature study, NMR analysis revealed a new product not observed in previous reactions at room temperature.[34] The reaction of 0.20 M "CH_3MgBr" with 0.020 M 2-MBP in the presence of 0.05 mole % $FeCl_3$ yielded after 7 hours at -30°, 44% pinacol, 15% addition and 41% of the new product. However, if the same reaction mixture was allowed to warm to room temperature prior to hydrolysis, 84% pinacol and 16% addition product was obtained. Thus the new product (41%) was converted to normal pinacol at room temperature. It was also found that when the reaction mixture was held at -30°, the new product was very slowly converted to normal pinacol. On the other hand, if the reaction was run at room temperature, 71% pinacol and 29% addition were obtained. If the hydrolyzed reaction mixture containing the new product was recombined with "CH_3MgBr" at room temperature, subsequent hydrolysis provided only pinacol (82%) and addition product (18%). Further studies

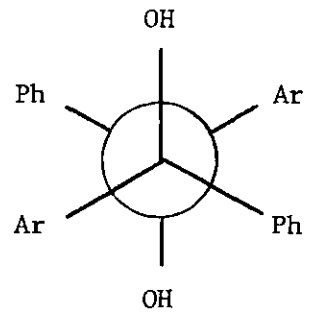
showed that lowering the temperature or increasing the amount of $FeCl_3$ both increased the amount of new product formed relative to other products. Thus, using 0.5 mole of $FeCl_3$ at -30°, 43% pinacol, 4% addition product and 53% new product were obtained.

After removal of the new product and the normal pinacol from the reaction mixture by washing with pet ether, the two were separated by column chromatography on silica gel with 10% $CHCl_3$ in pet ether. the new product was identified as a diastereomer of the pinacol on the basis of its spectral data (by Jerry D. Buhler)[34]. (See Experimental). Both compounds ("new product" and pinacol) had identical mass spectra and uv spectra. Their NMR and IR spectra were both very similar, but still distinctively different. Since the "new product" was detected only at low temperature,[45] it is apparently the kinetically formed pincacol. The pinacol normally seen at room temperature is then assigned to be the thermodynamic product.

In hopes of shedding some light on the actual mechanism of formation of the pinacols in the reaction with 2-MBP, it was desirable to determine which of the pinacol diastereomers is the threo form (2) and which is the erythro (3).



2



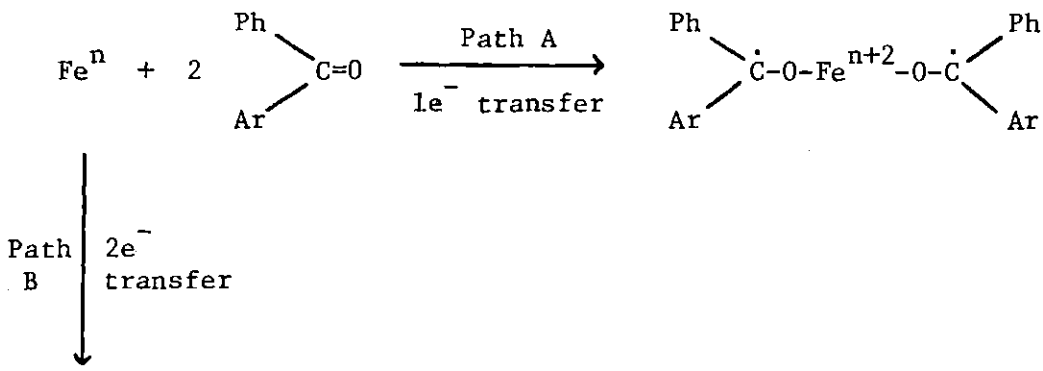
3

Since the preferred conformation of the threo form has a "cis-glycol" arrangement while the erythro has trans-hydroxyls in the preferred conformation, it was felt that the threo form would react more rapidly with reagents such as peracetic acid or lead tetraacetate. When 0.432 mmole of a 2,2'-dimethylbenzopinacol mixture (45% kinetic and 55% thermodynamic product) was allowed to react for 3 days with 0.158 mmole $Pb(OAc)_4$ (37% of theoretical) in acetic acid at room temperature (by Jerry D. Buhler)[34], NMR analysis after work up showed 55% thermodynamic pinacol, 34% kinetic pinacol and 11% ketone (30% conversion). Thus, the kinetic isomer reacted preferentially and therefore must be the threo form. The threo pinacol can of course, achieve a cis-OH conformation more easily that can the erythro isomer since the erythro isomer must bring the two largest groups (2-methylphenyl) together in order to do so.

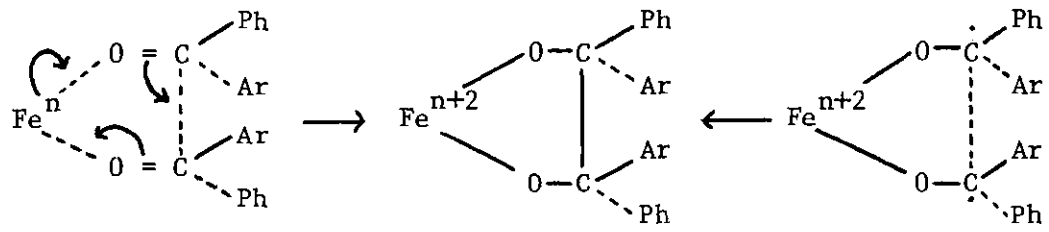
The question arises as to how the threo pinacol is formed and what

does its formation as the kinetic product reveal about the mechanism of iron catalyzed pinacol formation. It seems clear that iron catalysis is involved in the reduction of the ketone to the ketyl. The reduction could be a one electron reduction (path A) or a two electron reduction (path B); however, in either case, the threo iron pinacolate would be found with the larger 2-methylphenyl groups on opposite sides (eq. 3).

$$Fe^{n+2} + 2CH_3MgBr \longrightarrow Fe^{n} + 2CH_3\cdot + 2MgBr^{+} \qquad (2)$$

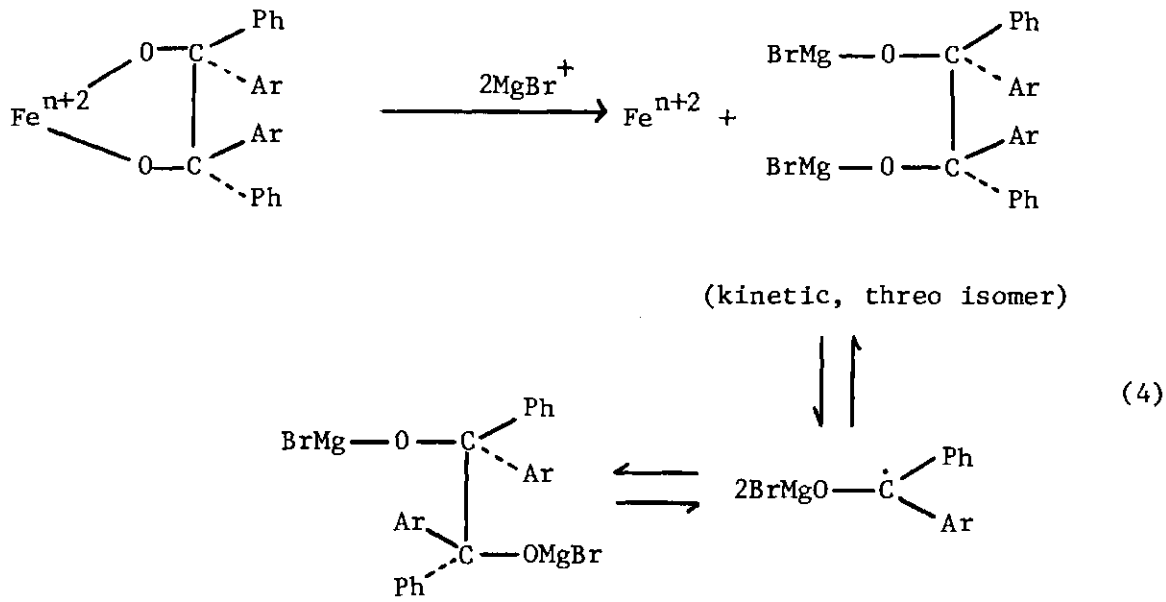


(3)



(threo product)

With either pathway the cyclic iron pinacolate could exchange with magnesium salts to form the bromomagnesium pinacolate followed by dissociation to the free ketyl and recombination to form the thermodynamically stable erythro isomer (eq. 4).

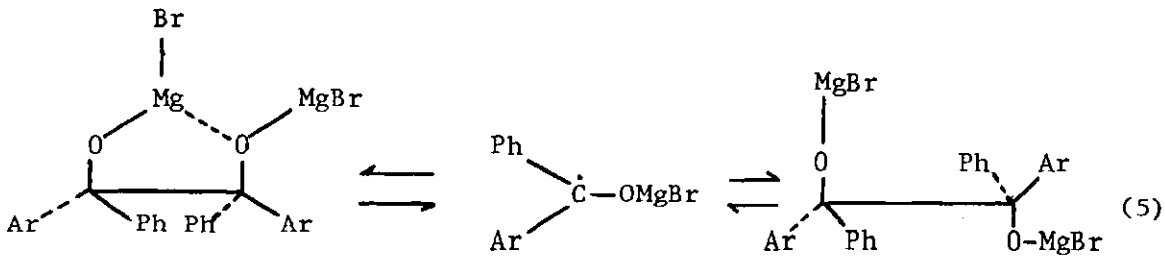


(4)

(thermodynamic, erythro isomer)

The initial efforts (by Jerry D. Buhler)[34] to convert the thermodynamic pinacol to the kinetic pinacol at low temperature in excess "CH_3MgBr" (in the presence or absence of $FeCl_3$) were largely unsuccessful, therefore, it was necessary to study the kinetic/thermodynamic pinacol equilibrium in detail. At room temperature this equilibrium lies almost entirely (97.5% or more) in favor of the thermodynamic product. At -25°, this is also true (95% thermodynamic pinacol). However, at -25°, the

approach to equilibrium from the side of the kinetic pinacol is very slow (Tables 7 and 8), whereas approach from the thermodynamic side is faster (Table 9). Furthermore, it appears that the pinacol mixture formed initially in the reaction of "CH_3MgBr" with 2-methylbenzophenone in the presence of $FeCl_3$ contains approximately equal amounts of kinetic and thermodynamic isomers. Only after the reaction is close to completion does the pinacolate show noticeable equilibration. It also appears that the presence or absence of $FeCl_3$ does not affect the equilibrium or the rate of approach to equilibrium (Figure 1). It seems, therefore that the equilibrium involved can be simply described by eq. 5, and that there



(5)

(Threo; Kinetic Product) (Erythro, Thermodynamic Product)

is no need to involve iron species in the pinacolate formation step.

A study of the reaction of "CH_3MgBr" with benzophenone in the presence of large amounts of $FeCl_3$ and $FeCl_2$ shows an enlightening trend. (Table 10). When "CH_3MgBr" and $FeCl_3$ are mixed in 1:1 ratio (exp. 5), no reaction occurs with the benzophenone. It is readily apparent that even as the $FeCl_3$ approaches this level (exp. 1-4), the percent

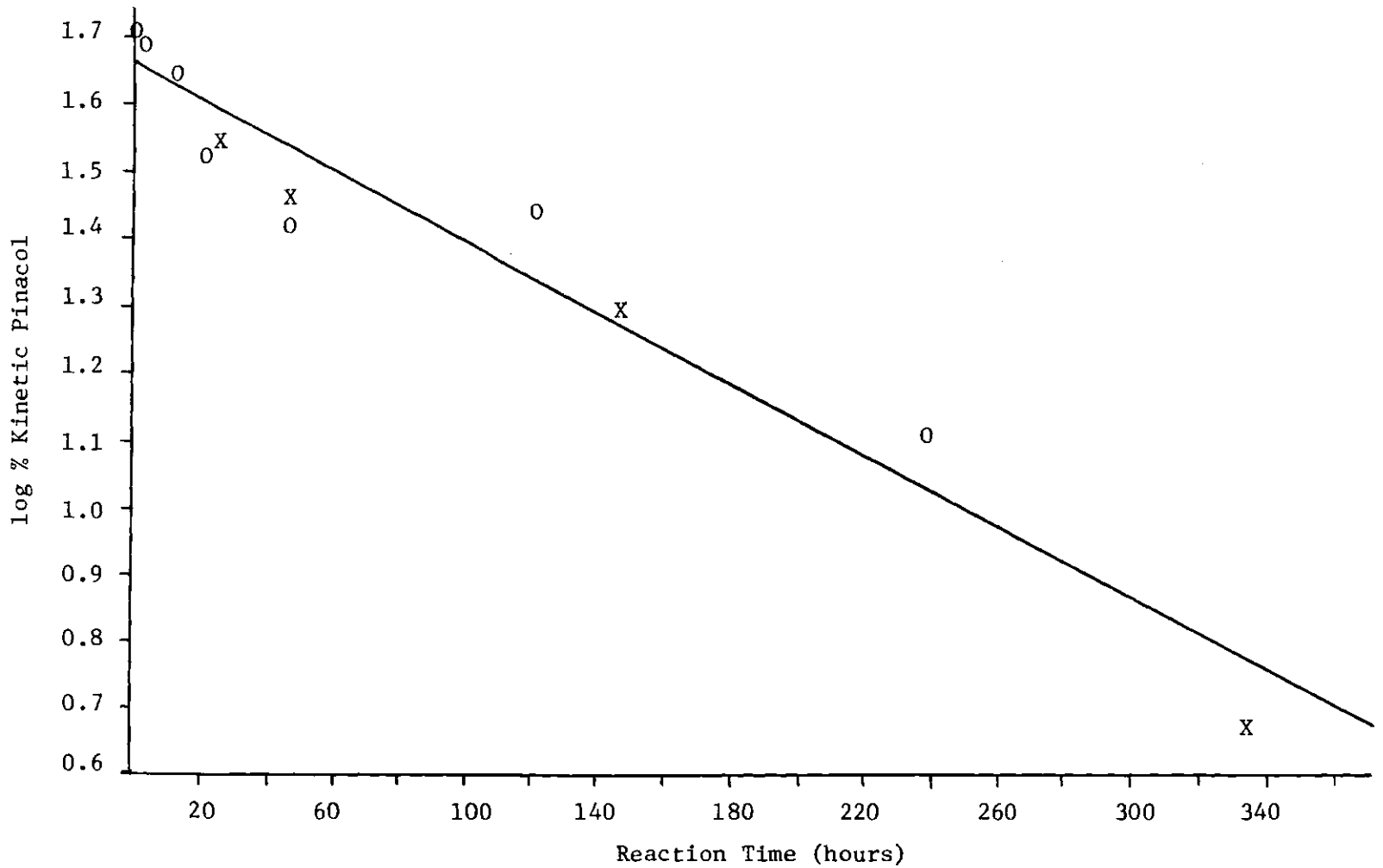


Figure 1. Rate of Approach to Kinetic Versus Thermodynamic Pinacol Equilibrium. O-Data From Table 13; Reaction Containg $FeCl_3$. X-Data From Table 9; No $FeCl_3$ Added; Time = Actual Time + 24 Hours to Stimulate Equivalent Starting Ratio of Pinacol Isomers.

reaction with the benzophenone decreases. When "CH_3MgBr" and $FeCl_2$ are mixed in ratios approaching 1:1.1 (exp. 6-8) no similar decrease in reaction with benzophenone is observed. This indicates that the species formed from the reduction of $FeCl_2$ by "CH_3MgBr" is capable of causing pinacol formation (or decomposing to a species capable of causing pinacol formation) while the species formed in the reduction of $FeCl_3$ is not. It is likely that the initial reaction between one equivalent of "CH_3MgBr" and one equivalent of $FeCl_3$ would involve exchange to give $\left[CH_3Fe^{III}Cl_2\right]$ (eq. 6) followed by homolytic decomposition to give hydrocarbons and an iron (II) species (eq. 7).

$$\text{"}CH_3MgBr\text{"} + FeCl_3 \longrightarrow \left[CH_3Fe^{III}Cl_2\right] + MgBrCl \qquad (6)$$

$$\left[CH_3Fe^{III}Cl_2\right] \longrightarrow CH_4 + C_2H_6 + C_2H_4, \text{ etc. } + \left[Fe^{II}Cl_2\right] \qquad (7)$$

If this is the case, then neither $\left[CH_3Fe^{III}Cl_2\right]$ nor the iron (II) species is capable of transfering an electron to the ketone to form the ketyl (and subsequently pinacol upon hydrolysis). It is equally apparent that if $\left[CH_3Fe^{III}Cl_2\right]$ is formed, it is not capable of addition to the ketone (it may decompose too quickly to react) and that the reaction of "CH_3MgBr" with $FeCl_3$ occurs too quickly for any reaction of "CH_3MgBr" with benzophenone to occur (since no 1,2-addition product is observed; Table 10, exp. 5).

On the other hand, it is likely that the initial reaction

between one equivalent of "CH_3MgBr" and one equivalent of $FeCl_2$ would involve exchange to give $\left[CH_3Fe^{II}Cl\right]$ (eqn. 8) followed by homolytic decomposition to give hydrocarbons and an iron (I) species (eqn. 9).

$$\text{"}CH_3MgBr\text{"} + FeCl_2 \longrightarrow \left[CH_3Fe^{II}Cl\right] + MgBrCl \qquad (8)$$

$$\left[CH_3Fe^{II}Cl\right] \longrightarrow CH_4 + C_2H_6 + C_2H_4, \text{ etc.} + \left[Fe^{I}Cl\right] \qquad (9)$$

If this is the case, either $\left[CH_3Fe^{II}Cl\right]$ or the iron (I) species transfers an electron to the ketone to form the ketyl (and subsequently pinacol on hydrolysis). Since the iron (II) species postulated above (eqn. 7) did not lead to pinacol formation, it seems unlikely that $\left[CH_3Fe^{II}Cl\right]$ would be capable of electron transfer either. This implicates the iron (I) species (eqn. 9) as the active agent leading to pinacol formation. Those Grignard reactions with benzophenone in the presence of trace amounts of iron would cycle this agent via a catalytic pathway (eqns. 10 and 11).

$$\left[Fe^{I}Cl\right] + Ph_2C{=}O \longrightarrow Ph_2\dot{C}{-}\bar{O}\ \left[Fe^{II}Cl\right]^{+} \qquad (10)$$

$$CH_3MgBr + Ph_2\dot{C}{-}\bar{O}\ \left[Fe^{II}Cl\right]^{+} \longrightarrow Ph_2\dot{C}{-}OMgBr + \left[CH_3Fe^{II}Cl_2\right] \qquad (11)$$

The results in Table 10 (exp. 8) also indicate 1,2-addition among the

products of the reaciton of "CH_3MgBr" with benzophenone in the presence of one equivalent of $FeCl_2$. There are two possible pathways whereby this could occur: $\left[CH_3Fe^{II}Cl\right]$ could react directly with the ketone to give 1,2-addition product (if the iron species does not decompose more rapidly than it adds to the ketone); or the rate of reaction of "CH_3MgBr" with $FeCl_2$ may be too slow to overwelmingly compete with direct Grignard reagent addition to the ketone to the exclusion of the latter. In light of the results in the case of the proposed $\left[CH_3Fe^{III}Cl_2\right]$ species, it seems that the latter possibility may be more likely.

The addition of large amounts of $MgBr_2$ to reaction 5 increases the amount of reaction with benzophenone (exp. 9 and 10). This implies that the active pinacol producing agent also involves magnesium, further complicating the mechanistically simple description shown in equations 6 through 11.

These data provide considerable insight into the mechanism of pinacol formation in Grignard reactions with ketones. The indication is that the free bromomagnesium ketyl is formed initially (probably through a SET step involving the iron as a catalyst [eq. 2]). The ketyl then couples indiscriminately with respect to steric effects (eq. 5) to give a statistical distribution of threo and erythro pinacolates. With time, equilibrium is established in which the more thermodynamically stable erythro isomer predominates.

The Nature and Mechanism of Hydrol Formation

The production of hydrols in reactions of "CH_3MgBr" with ketones is surprising since methyl Grignard reagents, having no β-hydrogen atoms, would generally not be considered capable of such reductions. Nevertheless, we have shown that when "CH_3MgBr" (prepared from Dow doubly sublimed magnesium) is allowed to react with 2-MBP, 2-methylbenzhydrol is formed. The amount of this product observed increases dramatically (Table 11) as the Grignard:ketone ratio increases. It is important to note that the amount of hydrol produced under a given set of conditions has been shown not only to depend on the grade of magnesium (Table 1) used to prepare the Grignard reagent, but also on the particular preparation from the same grade of magnesium. For example, different "CH_3MgBr" solutions, all made from Dow doubly sublimed magnesium using excess magnesium, when allowed to react with 2-MBP, formed 2-methylbenzhydrol in yields varying from 36% to 72%. However, for duplicate runs from the same Grignard solution, results are reproducible to within 3%. It has also been show (Table 1) that preparation of the "CH_3MgBr" from excess methyl bromide greatly decreases the ability of the Grignard to reduce benzophenone.

It is also important to note (Table 11) that when a constant amount of "CH_3MgBr" is allowed to react with decreasing amounts of ketone, the relative amount of 2-methylbenzhydrol produced increases with respect to the initial concentration of ketone; however, the absolute amount of hydrol remains constant (this observation has also been made by Rudolph and Smith[46]). These data indicate that the agent which produces the hydrol is used up stoichiometrically in the reaction. A low temperature

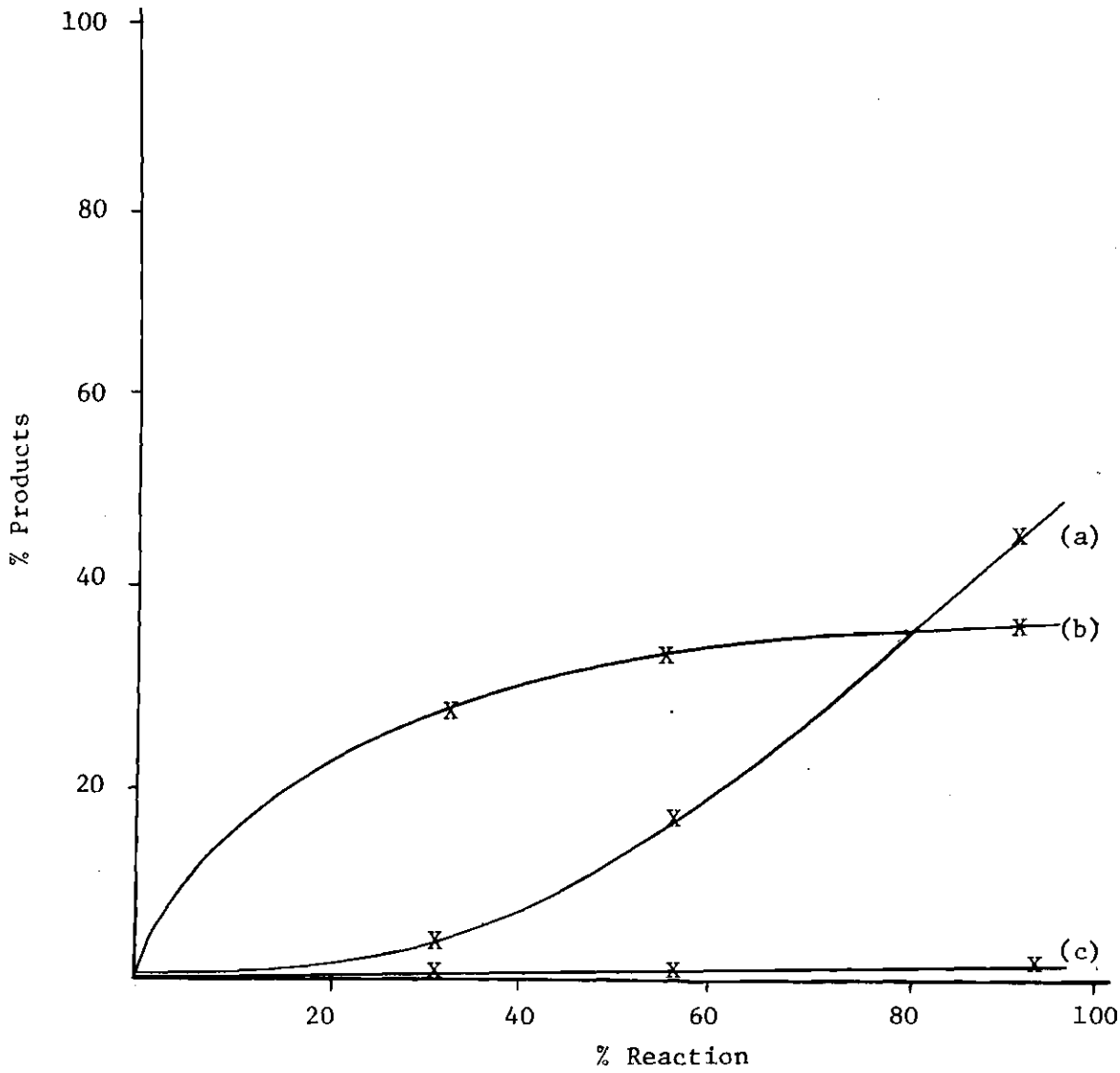


Figure 2. Reaction "CH_3MgBr" (0.50 M) With 2-MBP (0.00125 M) in Diethylether at -30 phenylethanol. (b) 2-methyl-benzhydrol. (c) 2,2-dimethylbenzopinacol.

product study (by Jerry D. Buhler)[34] makes this point dramatically (Table 12, Figure 2). For example, when "CH_3MgBr" (0.05 M) was allowed to react with 2-MBP (0.00125 M) at -30° and samples taken with time, the data clearly show that more than one reaction pathway is in operation and that initially the ketone is rapidly reduced to the hydrol before 1,2-addition becomes significant. From these observations, it is clear that the hydrol must be caused by some "impurity" (estimated 0.1-0.2%)[47] in the Grignard reagent.

Experiments (most carried out by Jerry D. Buhler) were run to determine the reaction conditions that affect the formation of hydrol. It was shown that the absolute reagent concentration and the reaction temperature has little effect on the product ratio.[34] It was also found that filtering the Grignard reagent before use had no effect on the amount of hydrol formed.[41] Addition of transition metal salts (Table 5) to reactions run under conditions which did not normally produce hydrol did not result in hydrol formation.[34] In addition, when those transition metals which have been shown to produce pinacol, were added to reactions run under conditions which normally did produce hydrol, pinacol formation was at the expense of hydrol formation.[34] The multiple regression and correlation analysis mentioned earlier (in connection with Table 1) showed no correlation between benzhydrol formation and transition metal content of the Grignard reagent.

With these results in mind, we turned out attention to an understanding of how the hydrol is formed. A number of pathways appear possible for this reaction. The Grignard could react with the ketone in

two successive SET steps to give the dianion which upon hydrolysis would form the hydrol (eq. 12). Alternatively, the Grignard could react in some sort of an alpha-elimination process to give an active hydride species which could serve as the reducing agent (eq. 13). It also is possible that the radical anion (eq. 14) or possibly the dianion (eq. 15) formed in the reaction of the ketone with the Grignard could extract a hydrogen atom or proton respectively from the solvent before

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \longrightarrow Ph_2\dot{C}\text{-}OMgBr \longrightarrow Ph_2\dot{\ddot{C}}\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (12)$$

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \longrightarrow [CH_2\text{:} + HMgBr] \longrightarrow Ph_2\overset{H}{\dot{C}}\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (13)$$

$$Ph_2\dot{C}\text{-}MgBr + (CH_3CH_2)_2O \longrightarrow Ph_2\overset{H}{\dot{C}}\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (14)$$

$$Ph_2\dot{\ddot{C}}\text{-}OMgBr + (CH_3CH_2)_2O \longrightarrow Ph_2\overset{H}{\dot{C}}\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (15)$$

$$[M\text{-}H] + Ph_2C{=}O \longrightarrow Ph_2\overset{H}{\dot{C}}\text{-}OM \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (16)$$

hydrolysis to give the hydrol. Another possibility involves the presence of an active hydride species in the Grignard reagent (or one produced rapidly in the Grignard reaction with ketones) which could directly reduce the ketone (eq. 16).

An investigation into these possibilities was carried out. When "CH_3MgBr" was allowed to react with 2-MBP in a 400:1 ratio (by Joe S. Bowers, Jr.)[35] and the reaction mixture quenched with 99.9% D_2O, no deuterium incorporation at the α-carbon was observed indicating that the hydrol is not a result of dianion formation followed by hydrolysis. Also when "CD_3MgBr" was allowed to react with 2-MBP (by Joe S. Bowers, Jr.)[35], no deuterium incorporation at the α-carbon was observed indicating the absence of a reaction as described by eq. 13. In a series of experiments the bromomagnesium ketyl was formed by the reaction of "CH_3MgBr" with 2,2'-dimethylbenzopinacol in 2:1 ratio and the resulting solution was altered in ways that produce a solution similar to that which exists in the reaction mixture involving the reaction of "CH_3MgBr" with 2-MBP. In the presence of Grignard:ketyl ratios ranging from 1 to 800, $FeCl_3$ ranging from 0.0 to 0.5 mole percent, and 1,2-addition product ranging from 0.0 to 1.0 equivalent, the ketyl upon hydrolysis yielded only 2,2'-dimethylbenzopinacol. In no case was any 2-methylbenzhydrol detected. These results indicate that neither the ketyl nor the dianion (possibly formed by the reaction of ketyl in excess Grignard reagent with iron catalysis, eqs. 14 and 15) can account for the formation of hydrol in the reaction of "CH_3MgBr" with 2-MBP.

In a separate series of reactions, "CH_3MgBr" was allowed to react with 2-MBP in $(CH_3CD_2)_2O$ (Table 13). An intermediate ketyl may be expected to abstract $D^{\bullet}$ from the alpha position of the solvent while the dianion would be more likely to abstract H^+ from the beta position. When "CH_3MgBr" was prepared in $(CH_3CD_2)_2O$ and the reaction with ketone carried out in the same solvent, all of the hydrol formed contained D on the α-carbon [$C_6H_5(C_7H_7)C(D)OH$]. This result shows that the hydrogen used in the reduction comes from the ether, and also provides further evidence that the dianion (eq. 15) is not an intermediate. However, when "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ was desolvated and redissolved in $(CH_2CD_2)_2O$ and the resulting solution allowed to react with 2-MBP, all of the hydrol produced was $C_6H_5(C_7H_7)C(H)OH$. This result demonstrates that the hydrogen abstraction from the ether does not take place when "CH_3MgBr" reacts with the ketone, but during the formation of the "CH_3MgBr". These data strongly indicate once again that the pathways described by eqs. 14 and 15 are not in effect. It appears that the hydrol producing species must be formed during the Grignard preparation step and that this species is more highly reactive as a reducing agent toward ketones than is the Grignard reagent as an alkylating agent (Figure 2). These experiments also indicate that the step involving the formation of the reducing species is radical in nature (since the α-D was abstracted from the ether in spite of the primary deuterium kinetic isotope effect involved.)

Since analysis of Dow doubly sublimed magnesium[48] shows no trace element or combination of trace elements in sufficient quantities (∿0.2%) to account for the amount of reducing agent necessary to form

benzyhydrol in up to 72% yield, it seems that the active reducing agent must be a magnesium hydride species. Although magnesium hydrides have never before been reported as by-products in the formation of a Grignard reagent, other members of our investigatory team have carried out several experiments which demonstrate that indeed this is the case. Table 14 illustrates[35] the striking similarity in reduction selectivity between an equimolar mixture of 2-MBP and acetone with "CH_3MgBr" prepared from Dow doubly sublimed magnesium and reduction of the same mixture with "CH_3MgBr" prepared from ROC/RIC magnesium crystals with added MgH_2. In both cases the reduction product is almost exclusively 2-methylbenzhydrol (98% vs. 94%). These results are very meaningful considering that "CH_3MgBr" prepared from ROC/RIC crystals yields no reduction product without added MgH_2. The fact that considerable reduction is observed in such a large excess of alkylating agent indicates that MgH_2 dissolved in Grignard reagent is a powerful reducing agent toward ketones.

Further evidence[35] that -MgH in the Grignard reagent is the source of the observed reduction is indicated by the similarity in observed stereochemistry when "CH_3MgBr" that gives reduction (Grignard prepared from Dow doubly sublimed magnesium) reduces 4-t-butycyclohexanone compared to "CH_3MgBr" that normally does not give reduction (Grignard prepared from ROC/RIC magnesium) except when MgH_2 is added to the reagent. The data in Table 15 show that the reduction of "CH_3MgBr" (Dow doubly sublimed) with 4-t-butycyclohexanone yields the reduction product in 89:11 ratio (equatorial:axial alcohol). On the other hand, "CH_3MgBr"

prepared from ROC/RIC magnesium which normally does not give any reduction product, produces a 79:21 ratio of alcohols (equatorial:axial) when MgH_2 is added. The similarity of the above stereochemistry is even more striking when compared to MgH_2 alone which gives a 32:68 ratio of reduction products.

A number of studies have indicated that Grignard formation is a radical process[49] involving the $CH_3\cdot$, $\cdot Mg^+$, and Br^- species. Combination of these species leads to "CH_3MgBr". From our data it is apparent that up to 0.2% of a radical species must react with ether to form an active hydride species. The following reaction is suggested:

$$CH_3CH_2OCH_2CH_3 + [\cdot MgBr] \longrightarrow [HMgBr] + CH_3\dot{C}HOCH_2CH_3 \qquad (17)$$

It was not initially apparent, though, why "CH_3MgBr" prepared from some grades of magnesium led to more hydrol that those samples prepared from other grades under the same reaction conditions (Table 1). Qualitatively it was noticed that the Grignard reagents prepared from large magnesium chips (Ventron chips and ROC/RIC crystals) gave little benzhydrol while those prepared from fine shavings (Dow doubly and triply sublimed) gave much more benzhydrol. In addition it was found that intermediate sized chips (Grignard grade turnings and Dow #5) of magnesium led to intermediate amounts of benzhydrol. A glance at Table 1 clearly indicates that much less hydrol formation is observed when the "CH_3MgBr" is prepared in excess methyl bromide. It became apparent to us that the methylbromide was capable of reacting with the active

hydride species during Grignard reagent formation thus using it up. Other members[35] of our research group, in order to test this point, reacted 2-MBP (0.3 mmole) with "CH_3MgBr" (120 mmole - ROC/RIC crystals) to which 0.2 mmole of MgH_2 had been added. The resulting product mixture contained 79% 2-methylbenzhydrol. The same reaction was carried out after addition of six drops of methyl bromide to the Grignard reagent prior to the addition of the Grignard reagent to the ketone. The resulting product mixture contained only 15% 2-methylbenzhydrol. A similar set of experiments was carried out using the "CH_3MgBr" prepared from Dow Doubly sublimed magnesium with no MgH_2 added. An equivalent set of results was obtained. It is clear, then that methyl bromide is capable of destroying the activity of both the dissolved magnesium hydride species that is formed in the preparation of the Grignard reagent and that added as MgH_2.

The size of the magnesium chips used in the Grignard preparation has a direct bearing on the amount of CH_3Br that builds up in the reaction mixture. Large magnesium chips have a relatively small surface area which allows CH_3Br to build up during the formation of the Grignard reagent, thereby destroying the magnesium hydride species. On the other hand, a much more finely divided grade of magnesium metal would be expected to react with CH_3Br much more rapidly than the larger magnesium chips thus avoiding a buildup of CH_3Br solution. Thus it is expected that the latter finely divided magnesium would produce a Grignard reagent that would result in more reduction of ketone to hydrol. It is also probable that the rate of addition of CH_3Br during

the preparation of "CH_3MgBr" would have an important effect on the hydride content of the resulting Grignard reagent. A rapid flow of CH_3Br would tend to cause Grignard reagents of low hydride content and slow CH_3Br addition would tend to form Grignard reagents of high hydride content. In preparation of "CH_3MgBr" for this study, no attempt was made to quantitatively control CH_3Br flow rates. The general procedure was to set the methyl bromide flow rate such that gentle ether reflux was maintained during Grignard formation. This, of course, necessitated the use of higher flow rates when forming "CH_3MgBr" from larger magnesium chips to maintain the same apparent rate of reaction.

In order to investigate the effect of the size of magnesium shavings used to prepare the Grignard reagent and the effect of methyl bromide flow rate, the following experiments were carried out (by Joe T. Laemmle and Joe S. Bowers, Jr.)[35]. A block of Dow Doubly sublimed magnesium was carefully milled with a new carbide tool to obtain fine shavings (approximately normal size for the Dow doubly sublimed magnesium we had been using) medium shavings (approximately Grignard grade turnings in size) and large chips (approximately ROC/RIC crystals in size). Methylmagnesium bromide was prepared from magnesium shavings of each size at a constant flow rate of 214 and 682 ml min^{-1} (Table 16). The slower flow rate was set such that gentle ether reflux was maintained in preparation of "CH_3MgBr" employing the fine shavings (i.e., a condition intended to maximize 2-methylbenzhydrol formation). The mass of magnesium was the same to within 0.1 g in all three preparations and the flow time was cut by one-third at the higher flow rate such

that the total amount of CH_3Br added was the same in all six preparations. The implications are clear. The percentage of 2-methylbenzhydrol found in the reactions decreases in a regular way at constant CH_3Br flow rate as the size of the magnesium shavings are increased and as the CH_3Br flow rate is increased. Thus the importance of excess CH_3Br during the preparation of the Grignard is very important in determining the amount of MgH_2 remaining in the Grignard reagent after its preparation.

General Mechanism of Grignard Reactions

In light of the present discussion, it seems that there are three pathways involved in the reaction of Grignard reagents with benzophenone:

$$-MgH + \phi_2C = O \longrightarrow \phi_2CHOH \tag{18}$$

$$RMgX + \phi_2C = O \xrightarrow{FeCl_3} \phi_2\overset{OH}{C}-\overset{OH}{C}\phi_2 \tag{19}$$

$$RMgX + \phi_2C = O \longrightarrow \phi_2\overset{R}{C}OH + \text{(substituted cyclohexadienyl)} + \phi_2\overset{OH}{C}-\overset{OH}{C}\phi_2 + \text{(substituted cyclohexadienyl)} + \phi_2CHOH \tag{20}$$

The first two pathways are now reasonably well understood; however the third pathway is still a matter of concern. The question remains, what is the mechanism of Grignard addition to ketones in the absence of any by-product producing impurities? From the work of Holm and Crossland[6] (and the work reported herein Table 3), it is apparent that the reaction of "t-BuMgCl" with benzophenone proceeds through a SET pathway represented by Holm in the following manner:

$$\text{t-BuMgCl} + \phi_2C{=}O \longrightarrow [\phi_2\dot{C}\text{-}O^-]MgBr^+ + \text{t-Bu}\cdot \longrightarrow \text{Products} \qquad (21)$$

In the reaction of "CH_3MgBr" with benzophenone the reaction pathway is much less obvious. While the SET pathway could indeed be operative (with the rate of collapse to give 1,2-addition product greatly exceeding the rate of $CH_3\cdot$ diffusion to produce pinacol), there is no real evidence to indicate that the pathway is not polar. The ability to "trap" this radical anion intermediate (or the species which has just donated the electron, i.e., the radical) would be instrumental in determining which mechanism may be involved.

With this in mind, styrene and p-dinitrobenzene (p-DNB) were screened as possible "trapping agents" in the reaction of "CH_3MgBr" with 2-MBP (Table 17). Styrene was not effective as a "trap". No products corresponding to $C_6H_5\text{-}C_3H_7$ were obtained. The styrene did polymerize more in the iron catalyzed reaction than in the uncatalyzed reaction, but this was true whether or not 2-MBP was present. Styrene had no effect on the expected product distribution in the

reaction of "CH_3MgBr" with 2-MBP. On the other hand, p-DNB did seem to have some effect on the reaction. The reaction without iron catalyst (exp. 7) was incomplete. Under the same conditions, this reaction without p-DNB went to completion (exp. 9). The iron catalyzed reaction (exp. 8) gave much less pinacol than was observed under the same conditions without p-DNB (exp. 10) and again failed to proceed to completion. Kornblum and coworkers[50] have pointed out that p-DNB is effective as a "radical anion scavenger" which can "short-circuit" SET reactions. Preliminary results (Table 17) indicated that p-DNB may be useful in probing Grignard reactions with ketones. If the Grignard reaction involves the process described by equation 22, it should be possible for p-DNB

$$RMgX + \phi_2C{=}O \longrightarrow [RMgX]^{+\cdot} + [\phi_2\dot{C}{-}\bar{O}] \longrightarrow \text{Products} \qquad (22)$$

to intervene as described by equations 23 and 24.

$$\text{p-DNB} + [\phi_2\dot{C}{-}\bar{O}] \longrightarrow \phi_2C{=}O + [\text{p-DNB}]^{-\cdot} \qquad (23)$$

$$[RMgX]^{+\cdot} + [\text{p-DNB}]^{-\cdot} \longrightarrow RMgX + \text{p-DNB} \qquad (24)$$

Thus, the starting materials are regenerated and the reaction is "short-circuited." It would be possible for SET products to "leak" through the circuit depending on the relative rates of the following reactions:

$$\underline{p}\text{-DNB} + [\phi_2\dot{C}\text{-}\bar{O}] \longrightarrow [\underline{p}\text{-DNB}]^{\cdot-} + \phi_2C{=}O \qquad (25)$$

$$[\phi_2\dot{C}\text{-}\bar{O}] + [\phi_2\dot{C}\text{-}\bar{O}] \longrightarrow \phi_2\text{-}\overset{\overset{\bar{O}}{|}}{\underset{\underset{\dot{O}}{|}}{C}}\text{—}\overset{\overset{\bar{O}}{|}}{\underset{\underset{\dot{O}}{|}}{C}}\text{-}\phi_2 \qquad (26)$$

$$[\phi_2\dot{C}\text{-}\bar{O}] + [RMgX]^{\cdot+} \longrightarrow \phi_2\text{-}\overset{\overset{R}{|}}{\underset{}{C}}\text{-}OMgX \qquad (27)$$

Step (23) above shows that p-DNB should be capable of removing an electron from the ketyl to regenerate the ketone. This concept was easily tested by the experiments described in Table 18. We have shown (here and earlier in this thesis) that the reaction of excess Grignard reagent with pinacol produces the corresponding ketyl, but that the Grignard does not further react with the ketyl. The only product upon subsequent hydrolysis is the starting pinacol (exp. 1 and 2). However, when pinacol is allowed to react with an equivalent amount of Grignard reagent in the presence of p-DNB, 27.4% ketone is recovered upon hydrolysis (exp. 3). If a 6:1 excess of the Grignard reagent is used, 42.4%, 1,2-addition product as well as 6.3% ketone is recovered (exp. 4). It is clear from these data that p-DNB is indeed capable of removing the electron from the ketyl radical anion to regenerate the ketone, although not with 100% efficiency.

It has been observed in the reactions involving p-DNB, that the p-DNB is never quantitatively recovered. This is undoubtedly due to a

side reaction in which p-DNB reacts directly with the Grignard reagent. Table 19 shows the results of a study to determine how much of the Grignard reagent is lost by reaction with p-DNB in this manner. The data indicate that ∿4 moles of "CH_3MgBr" and ∿6 moles of "t-BuMgCl" react with each mole of p-DNB. A complication, then, in the effect of p-DNB on Grignard reactions with ketones is the removal of some of the Grignard from the reaction, thus leading to incomplete consumption of the ketone.

Based on this information, a study was carried out to determine the effect of p-DNB on the rate of the reaction of "CH_3MgBr" with 2-MBP (Table 20, Figure 3). The reaction conditions were chosen such that after all the Grignard reacted with p-DNB (in experiments 5-8) there would still be as much Grignard left as in the reactions without p-DNB (exp 1-4). (It is important to note that this is a very qualitative correction, but one which provides a valid experiment. Initially, of course, the reaction which contains p-DNB will have a much higher Grignard reagent concentration than the equivalent reaction without p-DNB. If p-DNB has no significant effect on the reaction of "CH_3MgBr" with benzophenone, then the rate of the p-DNB containing reaction will be somewhat greater than the rate of the reaction in the absence of p-DNB, reflecting the initially higher Grignard reagent concentration in the former reaction. If, however, p-DNB does significantly intervene in the reaction of "CH_3MgBr" with benzophenone, a significant decrease in the rate of the reaction in the presence of p-DNB should be observed relative to the rate of the reaction in the absence of p-DNB.) It is

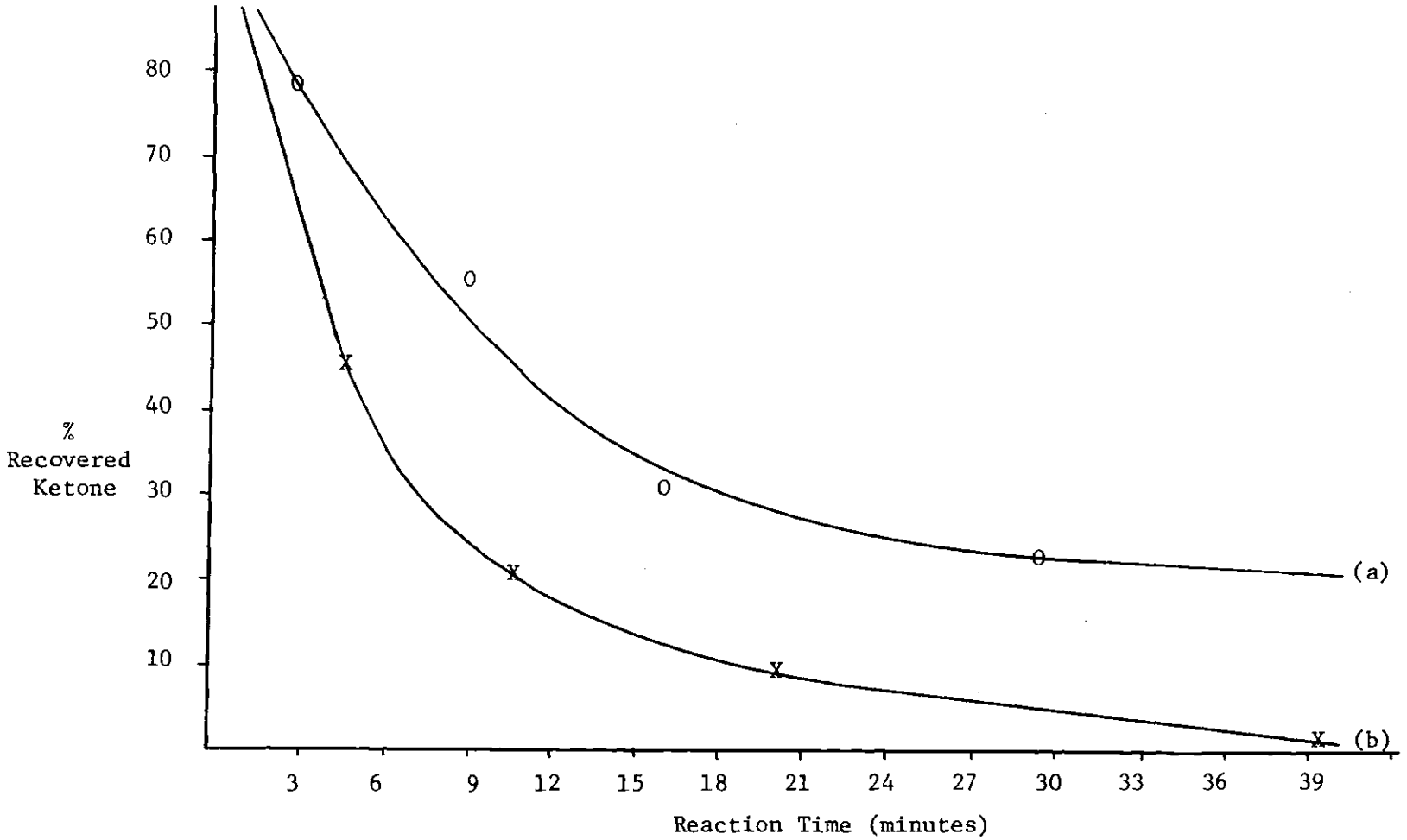
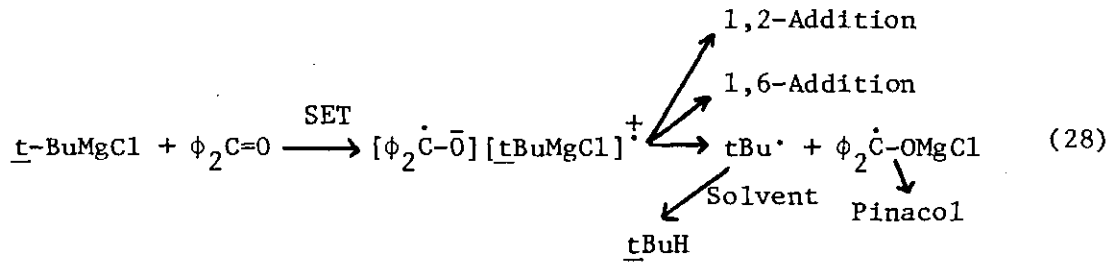


Figure 3. (a) Reaction of "CH_3MgBr" (0.033 M) With 2-MBP (0.0167 M) in Diethylether at Room Temperature. (b) Reaction of "CH_3MgBr" (0.100 M) With 2-MBP (0.0167 M) in the Presence of 17% p-DNB in Diethylether at Room Temperature.

apparent that the reaction of "CH_3MgBr" with 2-MBP in the presence of p-DNB is not significantly slower than the same reaction without p-DNB. (In fact, under the conditions chosen, the p-DNB containing reaction was actually slightly faster). In any case, the important feature of this set of reactions is that p-DNB completely eliminates pinacol formation. It appears that the p-DNB abstracts the electron from the ketyl to regenerate the starting ketone. The fact that the p-DNB cannot do the same to the 1,2-addition product is indicative of a difference in the mechanism leading to these two products.

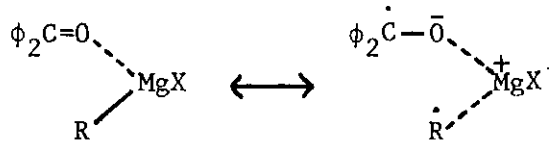
A similar experiment was conducted in order to determine the effect of p-DNB on the reaction of "t-BuMgCl" with 2-MBP (Table 21). The reactions were too fast for the methods of measurement that were used, however, this rapid rate in itself is enough to assure that p-DNB does not significantly slow the rate of reaction of "t-BuMgCl" with 2-MBP. The most impressive observation again concerns the formation of pinacol. While there is no pinacol formed in the p-DNB influenced reaction compared to $9.2\pm1.4\%$ formed in the absence of p-DNB, the ratios of 1,6-addition:1,2-addition products in the two reactions are identical (within experimental error). In the reaction of "t-BuMgCl" with 2-MBP the ratio of 1,6-addition:1,2-addition product is $84.1\pm 0.8\%:15.9\pm0.8\%$ while in the absence of p-DNB the ratio is $81.3\pm2.7:18.7\pm2.7$. These results indicate that there is some difference in the mechanism of formation of pinacol compared to the formation of the 1,2-and 1,6-addition products. The logical suggestion is that the pathway to pinacol formation must necessarily involve the "free ketyl"

which is susceptable to electron transfer to p-DNB. By analogy, then, the parthways leading to 1,2- and 1,6-addition must not involve the "free ketyl." In order to remain consistant with both the work of Holm and Crossland, as well as these new data, it seems necessary for the mechanism of the reaction of "t-BuMgCl" with 2-MBP to involve a radical anion-radical cation pair which can collapse to addition products or dissociate for form t-Bu· and pinacolate as described by equation 28:



(28)

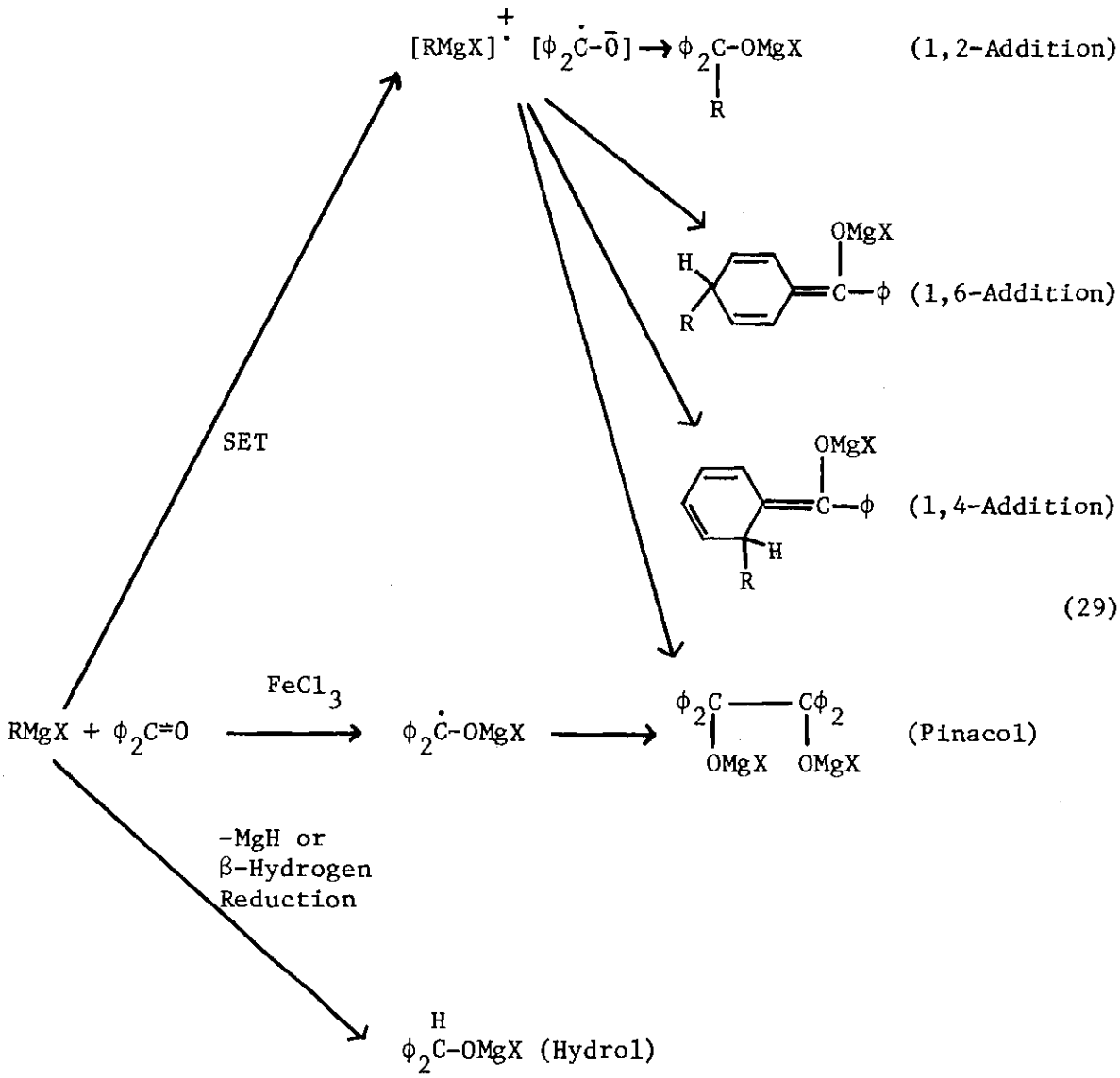
The radical anion-radical cation pair actually may be thought of as a charge transfer complex 4, originating via the σ-complex.



4

The tightness or looseness of this complex would undoubtedly be affected by the stability of the incipient radical, R·. This would in turn affect the amount of SET character observed in the reaction. It is possible, then, that all Grignard reactions with ketones proceed via this pathway.

With tert-butyl Grignard reagents, the complex is very loose due to the stability of the t-Bu$^{\cdot}$ radical, thus SET character is observed in the reaction, including the dissociation of the complex to give ketyl, which dimerizes to form pinacol. The methyl Grignard on the other hand, should form a tigher complex which bears less resemblence to a radical anion-radical cation pair. This complex could collapse to give only 1,2-addition too rapidly for anything else to occur (like diffusion of CH_3. to give pinacol). According to this picture, pinacol formation in the case of methyl Grignard reactions with benzophenones would be viewed as a separate reaction due only to the influence of traces of transition metal contaminants. The overall mechanism for Grignard reactions with benzophenones could be expressed by equation 29:


[RMgX]+· [φ2Ċ-Ō] → φ2C-OMgX
R
(1,2-Addition)
OMgX
H
R
C—φ
(1,6-Addition)
OMgX
C—φ
H
R
(1,4-Addition)
SET
(29)
RMgX + φ2C=O
FeCl3
φ2Ċ-OMgX
φ2C — Cφ2
OMgX OMgX
(Pinacol)
-MgH or
β-Hydrogen
Reduction
H
φ2C-OMgX (Hydrol)

Hydrol would normally be formed only when the R-group has β-hydrogens and when other factors are favorable (i.e. steric bulk, reduction potential, radical stabilities, etc.) or when -MgH species are present in the Grignard reagent. Pinacol would occur both from dissociation of the radical anion-radical cation pair (e.g. when R=tBu) and from direct action of an iron-magnesium species of the ketone (e.g. when R=Me). All other products would come about only through the radical cation radical anion pair.

The reaction of "t-BuMgCl" with benzophenones apparently occurs only by the SET pathway, even in the presence of $FeCl_3$. Most likely the rate of the reaction along this pathway greatly exceeds that along the other pathways due to the reduction potential of the ketone and the radical stability of the R-group of the Grignard reagent. There may be another factor, however. It is possible that "t-BuMgCl" does react with $FeCl_3$ in a manner similar to the reaction of "CH_3MgBr" with $FeCl_3$, but that the initially formed intermediate in the former case does not lead to a pinacol forming species (i.e. one capable of SET). In the reaction of "t-BuMgCl" with $FeCl_3$, a t-Bu-Fe- species would be expected, unlike the CH_3-Fe- species, to decompose by olefin elimination to give an intermediate -Fe-H compound (before further decomposition). It is plausable that this -Fe-H intermediate would not be as capable of transferring an electron to the ketone as would the iron species which was proposed in the methyl Grignard reaction with $FeCl_2$. On the other hand, it is also reasonable that if such an -Fe-H intermediate is formed, it could be stable enough to effectively tie up the iron such that any species further

along the decomposition pathway that may be capable of SET (to give pinacol) has no chance to compete with the rapid Grignard reaction. It may be of interest to point out that the reaction of "neopentylmagnesium bromide" with benzophenone in diethylehter in the presence of trace amounts of $FeCl_3$ leads almost exclusively to pinacol while the same reaction in the absence of $FeCl_3$ leads equally exclusively to 1,2-addition product. (Work carried out by Daniel Campbell)[44]. A neopentyliron species, like a methyliron species, would be incapable of olefin elimination to give an iron hydride type compound, and so would be expected to decompose via a homolytic pathway. Thus both methyl and neopentyl Grignard reagents apparently react with iron to give species which are incapable of olefin elimination, but which lead to pinacol formation, whereas the t-butyl Grignard reagent apparently reacts to give a species which would probably decompose via an olefin elimination pathway, but which does not lead to pinacol formation. While this suggestion cannot be proven, it does provide a reasonable explanation of the result. (Just exactly how this proposed iron hydride species could come about will be discussed in greater detail in the next section with respect to the reaction of "t-BuMgCl" with acetone in the presence of $FeCl_3$).

If the above mechanistic picture described by equation 29 is valid, steric factors in the vicinity of the reaction site would be expected to show up in the product distribution of the reactions of "CH_3MgBr" with benzophenones in the presence of $FeCl_3$. Table 22 shows that this is so. The reaction with 2-MBP in the presence of 4000 ppm

$FeCl_3$ shows 11.5% more pinacol than the same reaction with benzophenone. This would have been predicted since the addition reaction has the largest steric requirement and therefore would occur at a slower rate in the raction with the bulkier ketone. The rate of electron transfer from the iron species to produce pinacol would not be nearly so affected by steric bulk, so that SET would occur at about the same rate with each ketone. It appears from experiments 2 and 4 that this effect is less noticeable at higher iron concentration (only 6.9% with 40,000 ppm Fe).

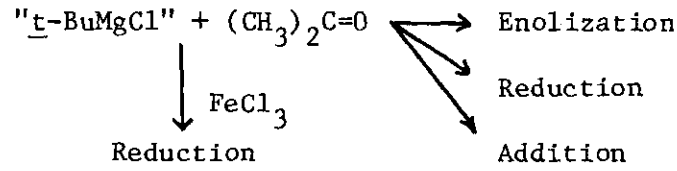
Grignard Reactions with Fluorenone and Acetone

The reduction potential of the ketone involved in reactions with Grignard reagents should play a large role in determining the amount (if any) of SET involved in the reaction. Reactions utilizing fluorenone and acetone were carried out to probe this possibility. Table 23 shows that the reactions of Grignard reagents with fluorenone (reduction potential = -0.87V versus SCE in Formaldehyde[51]; -1.29V versus SCE in DMF[52]) are qualatatively very similar to those with benzophenone (reduction potential = -1.26V versus SCE in formaldehyde[51]; -1.72V versus SCE in DMF[53]; -1.31V versus SCE in 50% Ethanol/H_2O, pH 8.5[53]). The reaction of "CH_3MgBr" with fluorenone in the presence of 4000 ppm $FeCl_3$ (exp. 2) shows less pinacol formation than the same reaction with benzophenone (29.4% versus 46.0%). The reaction of "t-BuMgCl" with fluorenone (exp. 4) shows about the same amount of pinacol as a similar reaction with benzophenone (9.8% versus 9.7%) but more 1,2-addition and less 1,6-addition (74.8% and 15.4% versus 42.3%

and 48.0%). Both sets of results can be easily explained in terms of steric bulk at the reaction site. The structural difference between fluorenone and benzophenone is the bond in the ortho position of the fluorenone rings which pins the rings back from the carbonyl position. This position is therefore more open to attack in the fluorenone molecule than in the benzophenone. In the case of methyl Grignard reactions 1,2-addition to fluorenone is thus able to compete more favorably with iron catalyzed pinacol formation and in the case of tert-butyl Grignard reactions, coupling at the 2-position takes place more readily than coupling at the 6-position. The relative amount of diffusion to form pinacol in the tert-butyl Grignard reaction is obviously about the same with each ketone since about the same amount of pinacol is observed in each case. The effect of $FeCl_3$ catalyzed Grignard addition to fluorenone is qualitatively similar to that observed with benzophenone: it causes pinacol formation in the methyl Grignard reactions and has no effect in tert-butyl Grignard reactions. The effect of HMPA upon these reactions is also qualitatively the same as with benzophenone; HMPA favors 1,2-addition with tert-butyl Grignards and has little effect upon methyl Grignard reactions. Other members of our group[35] have shown that qualitatively similar results are obtained from ketones and quinones of even lower reduction potential.

Reactions of Grignard reagents with acetone (reduction potential -2.46 V versus SCE in 75% Dioxane/H_2O[53]) have resulted in a trend different from the one observed in the cases of benzophenone and fluorenone (above). (Table 24). Experiments 1-6 show that "CH_3MgBr"

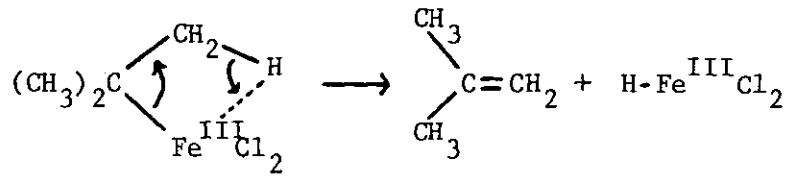
reacts with acetone to give only 1,2-addition product regardless of the grade of magnesium, the mode of Grignard preparation or the addition of 4000 ppm $FeCl_3$. Apparently the reduction potential of the acetone is high enough that the iron species that would be expected to generate pinacol is unable to transfer an electron to the ketone. The reaction of "t-BuMgCl" with acetone, on the other hand, shows variations depending on the $FeCl_3$ content of the reaction. When no $FeCl_3$ is added (exp. 7 and 8), the % 1,2-addition varies from 55.6 to 62.1%, the % reduction varies from 15.7 to 8.4%, and the % enolization varies from 28.7 to 29.5% depending on the purity of the magnesium used to prepare the Grignard reagent. In the presence of 4000 ppm FeCl, however, the % 1,2-addition varies from 5.1 to 17.1%, the % reduction from 87.8 to 73.9% and the % enolization from 7.1 to 9.0%. It could be that while "CH_3MgBr", "$CH_3MgBr + FeCl_3$" and "t-BuMgCl" are unable to donate an electron to a ketone with a reduction potential as high as that of acetone, "t-BuMgCl + $FeCl_3$" is capable of such SET. On the other hand, it is possible that the intermediate species postulated previously for the reaction of "t-BuMgCl" with $FeCl_3$ is rapidly reacting with the acetone in competition with the normal Grignard reaction (30):



(30)

It seems reasonable that the intial reaction between "t-BuMgCl" and $FeCl_3$ would involve exchange to give t-Bu-$Fe^{III}Cl_2$ (eq. 31) which could be expected to decompose via olefin elimination to give an intermediate iron hydride species (eq. 32).

$$\text{"t-BuMgCl"} + FeCl_3 \longrightarrow \text{t-Bu-}Fe^{III}Cl_2 + MgCl_2 \qquad (31)$$



(32)

It is likely that such a species would be capable of reducing acetone (eq. 33), probably followed by exchange with $MgCl_2$ to complete the catalytic cycle (eq. 34).

$$HFe^{III}Cl_2 + (CH_3)_2C{=}O \longrightarrow (CH_3)_2CH{-}OFeCl_2 \qquad (33)$$

$$(CH_3)CH{-}OFeCl_2 + MgCl_2 \longrightarrow (CH_3)_2CH{-}OMgCl + FeCl_3 \qquad (34)$$

A relative rate study of the reaction of "t-BuMgCl" with acetone in the presence or absence of 4000 ppm $FeCl_3$ (Table 24, entries 11-20) casts some light on the above suggestions. The 20 minutes samples (entires 8 and 10) were used to determined the relative % enolization: % 1,2-addition for each reaction: 0.526 for the iron catalyzed reaction and 0.475 for the uncatalyzed reaction. Assuming that in each of these reactions the % enolization is a constant fraction of the % 1,2-addition (with time), the plots of % unreacted acetone versus time seen in Figure 4 were constructed. It is readily apparent that the iron catalyzed reaction is quite a bit faster than the uncatalyzed one.

From Figure 4 it can be determined that the half life of the reaction of 0.093 M "t-BuMgCl" with 0.063 M acetone in the presence of 4000 ppm $FeCl_3$ is about 10 seconds and the half life of the same reaction without $FeCl_3$ is about 30 seconds. The significance of this observations is that although the iron catalyzed reaction is about 3 times as fast as the uncatalyzed one, it produces only about 1/3 as much 1,2-addition product and about 1/3 as much enolization. It seems that the real difference between the two reactions is a competition such as the one involved in equation 30. The rates of 1,2-addition and of enolization are unaffected by the addition of $FeCl_3$; however, in the presence of $FeCl_3$, a species may be formed (presumably an iron hydride) which rapidly reduces acetone via a pathway in competition with the normal (polar) Grignard reaction.

In summation then, it appears that methyl Grignard reagents react with benzophenone, fluorenone, and acetone via a polar pathway.

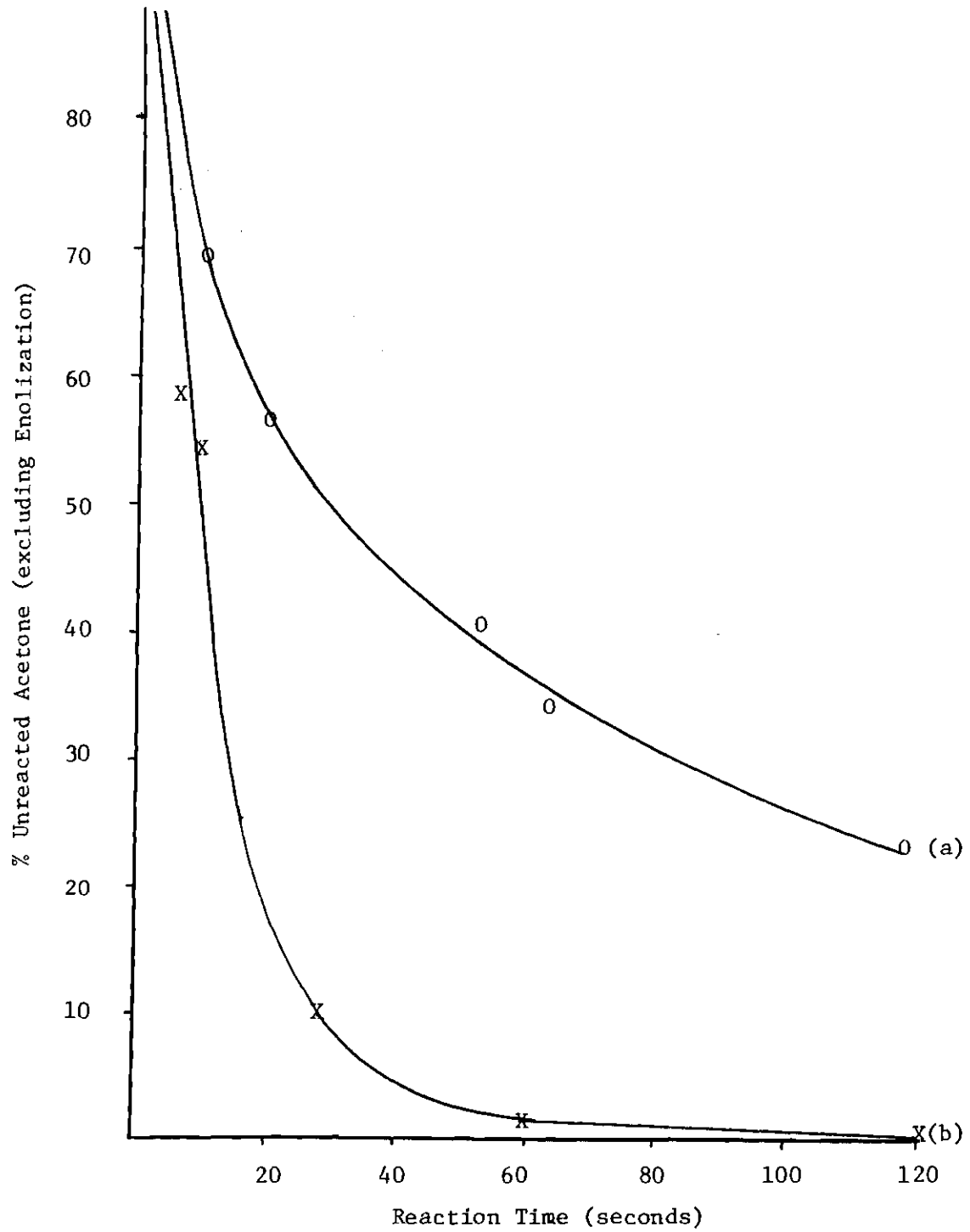


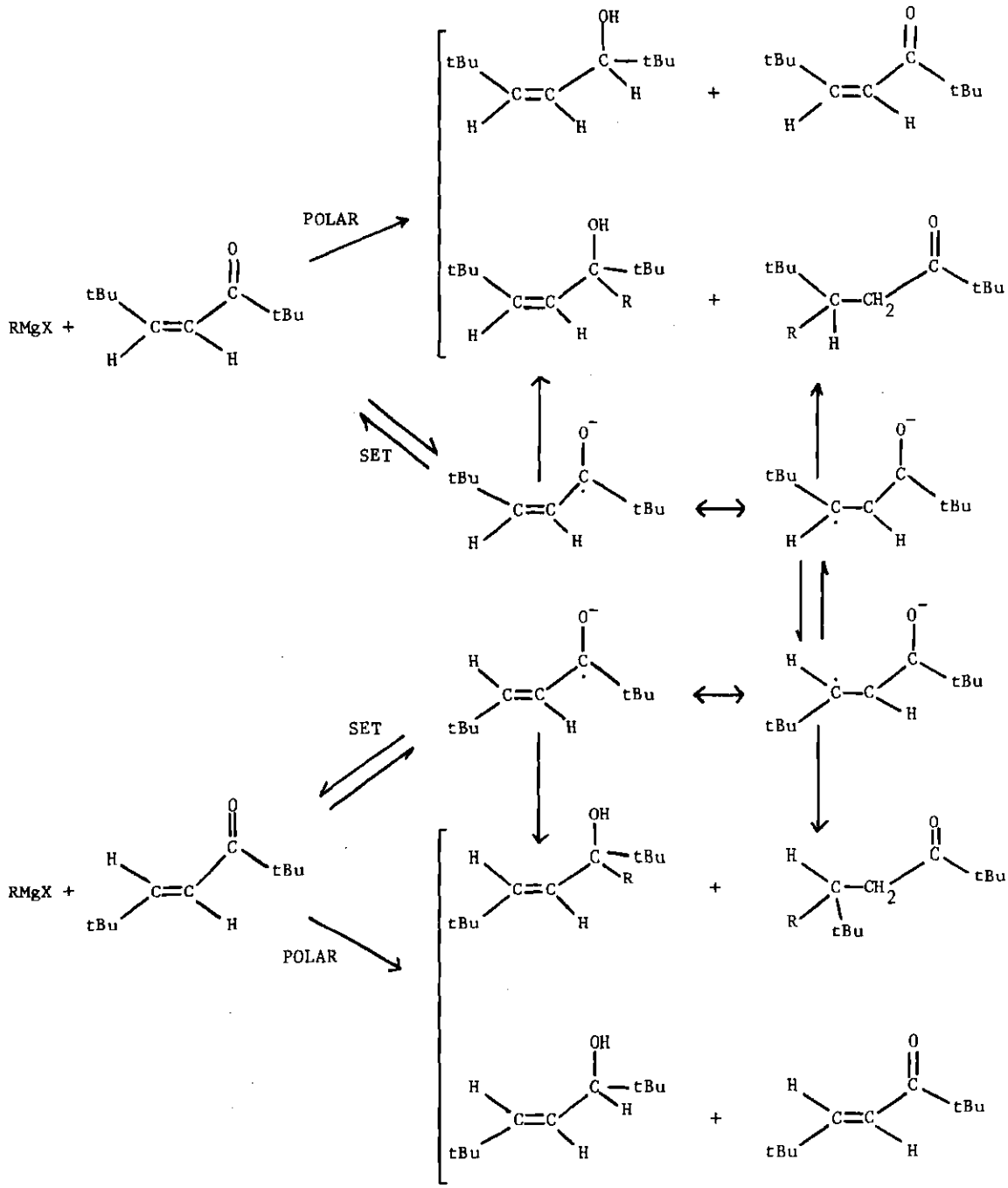
Figure 4. (a) Reaction of "t-BuMgCl" (0.093 M) With Acetone (0.063 M). (b) Reaction of "t-BuMgCl" (0.093 M) With Acetone (0.063 M) in the Presence of 4000 ppm $FeCl_3$. Both Reactions in Diethylether at Room Temperature.

In the presence of $FeCl_3$, however, methyl Grignard reagents give rise to a species which is capable of transfering electrons to benzophenone and fluorenone but not to acetone. Tert-butyl Grignard reagents seem to react with benzophenone and fluorenone by SET and with acetone via a polar pathway. Ferric chloride apparently reacts with "t-BuMgCl" to produce a species which is unable to compete with Grignard addition to benzophenone or fluorenone, but which reduces acetone at a rate about three times faster than the Grignard reaction with acetone. Presumably, the active reagent in this reduction is an iron hydride species. Whether this reagent reacts via a polar or SET mechanism is not known, but since it competes more easily with the "t-BuMgCl" for acetone than for benzophenone, it is likely to react by a polar pathway. In any case, it appears that the 1,2-addition product formed by the reaction of "t-BuMgCl" with acetone comes about through a polar pathway both in the presence and in the absence of $FeCl_3$.

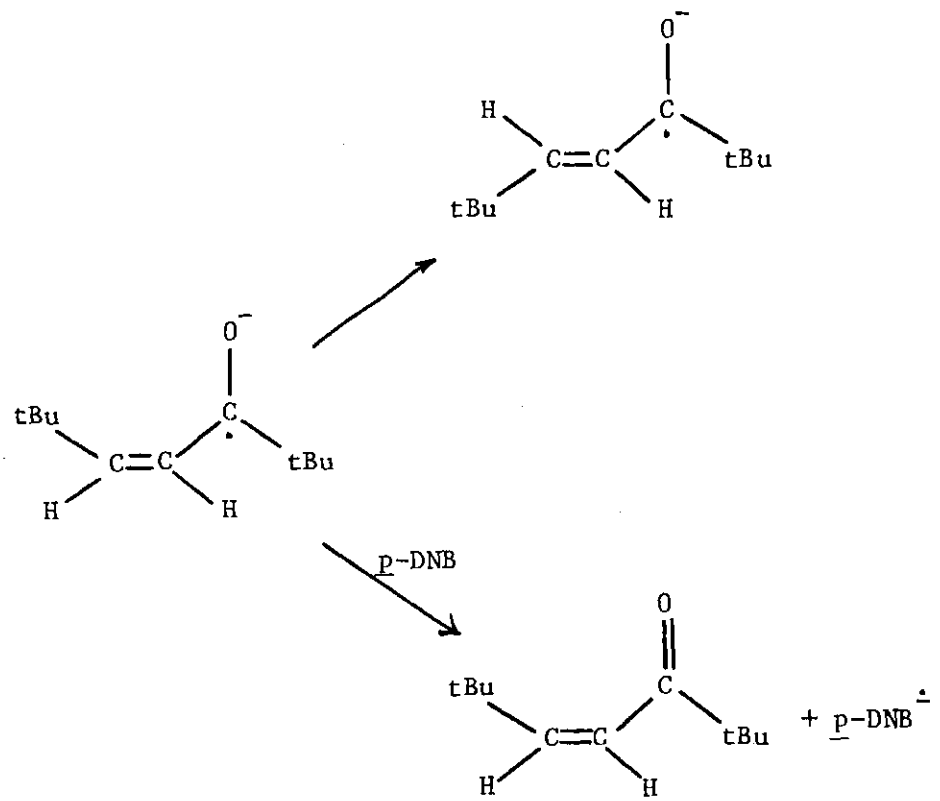
Reactions with 2,2,6,6-Tetramethylhept-4-ene-3-one

General Introduction

The idea underlying the use of 2,2,6,6-tetramethylhept-4-ene-one as a probe is that the cis-iomer is rapidly converted to the trans-iomer in any reaction involving the transfer of an electron to the enone.[54] A polar reaction, however, involving the cis-isomer would be expected to give only cis-products (see eq. 35). Thus this enone can be used as a probe in an attempt to detect SET when allowed to react with Grignard reagents. The experiments in this thesis generally involve two equivalents of enone per equivalent of organometallic reagent.


RMgX +
POLAR
SET
SET
POLAR
RMgX +
tBu
OH
O
R
H

This allows observation of "unreacted enone" which, presumably, has been involved in the SET equilibrium and may reflect the amount of SET occurring in the reaction. The major drawback to the use of this enone as a probe involves the isomerization of the starting "cis-enone" through a SET pathway not necessarily along the main reaction pathway, followed by a polar reaction to give what appears to be products of a SET reaction (see eq. 35). Based on information gained from the reactions of Grignard reagents with benzophenones in the presence of p-DNB, it seems that it may be possible to inhibit isomerization of "cis-" to "trans-enone" by the addition of p-DNB to the "enone" reactions (eq. 36).



(36)

There are other subleties concerning this probe which must also be considered. If the reaction of a Grignard reagent with "cis-enone" proceeds via a polar pathway, only cis-addition product will be observed. If, however, the reaction pathway involves SET, there are three possible observations. If the rate of isomerization of the "cis-ketyl" to the "trans-ketyl" is faster than the rate of collapse of the SET intermediate (such as the radical cation-radical anion pair) to give products (see eq. 35), trans-addition products will be observed. If, on the other hand, the rate of collapse to give products is faster than the rate of isomerization of "cis- to trans-ketyl", then only cis-addition products will be observed, in spite of the SET pathway. If the rate of collapse to give products and the rate of isomerization of "cis- to trans-ketyl" are comparable in rate, a mixture of cis- and trans-addition products will be observed. For this reason, then, it is extremely difficult to observe any difference between a polar reaction and a SET reaction in which collapse to give addition products is faster than ketyl isomerization.

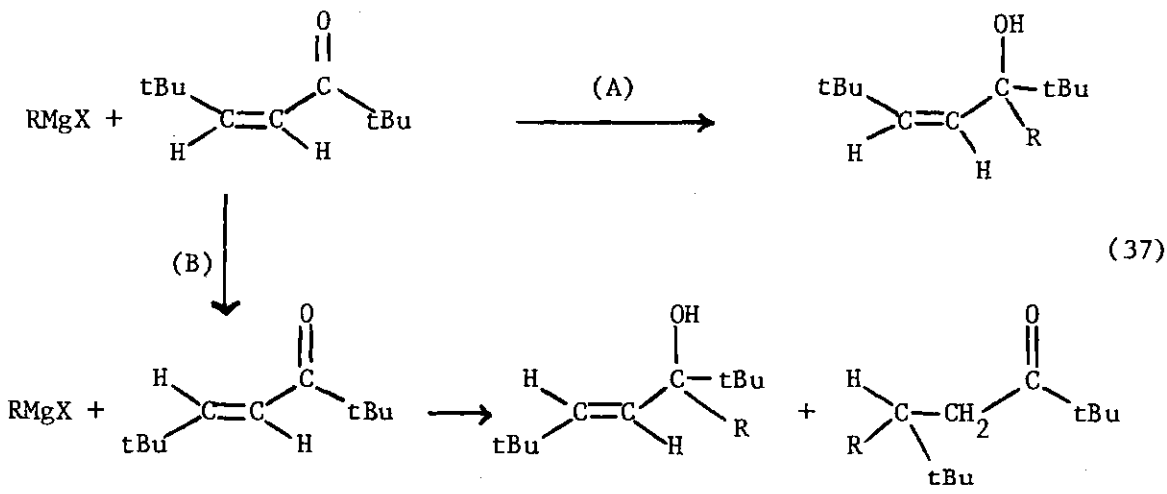
In spite of the potential drawbacks of this system, a study of the reaction of cis- and trans-2,2,6,6-tetramethylhept-4-ene-3-one with various Grignard reagents and other organometallic compounds was carried out. The hope was that by careful comparison of the various reactions, insight could be gained into the mechanism of Grignard reactions with ketones, especially with respect to the mechanism of formation of the 1,2-addition product.

Reaction of Various Magnesium Compounds with "cis-Enone"

The initial study (Table 25) was designed to discover the optimum reaction conditions. It was observed (entires 7-10) that $MgBr_2$ itself (which is a component of the Schlenk Equilibrium making up the Grignard reagent) is capable of isomerizing the "cis-enone". This would tend to invalidate the probe, however, a comparison of entires 1 and 7 shows that the Grignard reaction is completely over before 4% isomerization due to $MgBr_2$ is observed. The $MgBr_2$ then should have no real effect on the results of the Grignard reactions with the "enone". The reaction of $(CH_3)_2Mg$ with "cis-enone" shows some isomerization in this time period. The reaction of $(CH_3)_2Mg$ with "enone" will be discussed in more detail in a later section (with respect to Table 29). The twenty minute reaction time was chosen as the most effective time period that would still be convenient. It is used in most of the rest of the experiments in this section.

The reaction of "CH_3MgBr" with excess "cis-enone" is shown to result in both 1,2- and 1,4-addition to the enone with various amounts of isomerization depending upon the grade of magnesium from which the Grignard reagent was made (Table 26, entries 1, 2 and 4). Addition of increasing amounts of $FeCl_3$ to the reaction results in increasing amounts of isomerization observed in the products, as well as in the "unreacted enone" (entires 4-7). The reaction of "CH_3MgBr" with trans-enone" (entry 3) yields only 1,4- and 1,2-trans-addition, as may have been expected. It is interesting to note, however, that whether one begins with the "cis-" or "trans-enone", the ratio of % 1,4-addition:

%1,2-trans-addition is about the same, regardless of the amount of 1,2-cis-addition produced in the reaction. It seems almost as though two separate processes are involved: the addition of the Grignard reagent to the "cis-enone" to form 1,2-cis-addition product (path A) and the isomerization of the "enone" followed by Grignard addition to form 1,2-trans-addition and 1,4-addition in about 51/49 ratio (path B) (eq. 37).



(37)

The analogy to equation (39) in the case of Grignard reactions with benzophenones and equation (30) in the case of Grignard reactions with acetone is obvious. The isomerization of the enone in this reaction is probably due to the transition metal impurities in the magnesium. What can be said about the mechanism of the addition reaction is not as obvious. This topic will be further discussed a little later.

The reaction of "t-BuMgCl" with excess "cis-enone" (Table 26, entires 8 and 9) shows almost complete isomerization of both starting

materials and products, indicative of a SET reaction. The explanation offered previously (eq. 37) again seems to be true: the 1,4-addition: 1,2-trans-addition ratio does seem to remain constant (about 30/70 ratio) even when the reaction is carried out with "trans-enone" (entry 11). However, there is never really enough 1,2-cis-addition product produced to make the comparison as compelling in this case as in the methyl Grignard case. It is interesting to note that the addition of 40,000 ppm $FeCl_3$ to the reaction of "t-BuMgCl" with "cis-enone" (entry 10) results in a 6% increase in the amount of 1,2-reduction observed, reminiscent of the unusual increase in reduction product observed with acetone in the presence of $FeCl_3$. The increase in the "enone" reduction product with "t-BuMgCl" is considerably smaller than the increase in reduction product observed in the "t-BuMgCl"reaction with acetone, especially considering the tenfold increase in ppm $FeCl_3$ used in these "enone" experiments. However, this result points out that the reaction competing with the reduction by a postulated intermediate iron hydride species is faster (relatively) in the "enone" reaction than in the acetone reaction. It is also interesting to note that the reaction of "t-BuMgCl" with "trans-enone" yields 2.3% "cis-enone" in the product mixture (entry 11), possibly indicative of a "cis-to trans-ketyl" equilibration which, of course, lies far to the side of the "trans-ketyl". All of the data concerning reaction of the "cis-enone" with "t-BuMgCl" tends to lend credence to the theory that the reaction proceeds predominantly through a SET pathway.

The reaction of "allyl MgBr" with excess "cis-enone" seems less

complicated. It produces almost only 1,2-cis-addition product and does not significantly isomerize the remaining "cis-enone" starting material (Table 26, entry 12). The addition of 40,000 ppm $FeCl_3$ (entry 13) isomerizes the starting enone somewhat, but has only a small effect on the isomerization of the 1,2-addition product. This isomerization may be occurring via a route not related to the major reaction pathway (such as (B) in equation 37) after the addition of "allyl-MgBr" to the "cis-enone" has already occurred, since only the excess starting "enone" is affected (and not the addition products). In any case, the addition reaction is probably occurring too rapidly for the iron to have much effect. Reaction of the "allyl-MgBr" with "trans-enone" produces only 1,2-trans-addition. In no case is any 1,4-addition observed. The allyl Grignard reaction, therefore, appears to be a straight forward case of polar addition to the "enone". There remains the possibility, however, that the reaction proceeds by SET due to the fact that 1,2-addition proceeds more rapidly than the isomerization of the ketyl from cis- to trans-. However, since "allylMgBr" reactions with benzophenone only three times faster than "t-BuMgCl" and the latter shows essentially complete isomerization when reacted with the "enone", it is clear that the allyl Grignard should exhibit significant isomerization when reacting with the same "enone" if indeed SET is the reaction pathway. Since the allyl Grignard exhibits not more than a trace of isomerization of the enone or the 1,2-addition product, one must conclude that the allyl Grignard reaction most probably proceeds via a polar pathway.

It is important to note that the control experiment in which $FeCl_3$ equivalent to the 40,000 ppm used in the Grignard reactions with "cis-enone" was carried out (entry 16). No isomerization of the "cis-enone" was observed under these conditions in the absence of Grignard reagent.

Relative Rates of Methyl Grignard Reactions with "cis- and trans-Enones"

In order to help further unravel the complicated reaction of "CH_3MgBr" with "cis-enone", a qualitative rate comparison was made between the reaction of methyl Grignard with "cis- versus trans-enone". (Table 27; Figure 5). It is readily apparent that "CH_3MgBr" reacts much more rapidly with the trans- than with the cis-isomer. This fact, along with a pathway involving isomerization of the "cis-enone", such as path (B), equation 37, would easily explain the predominance of isomerized 1,2-addition product. Note in Table 27, entries 1-8 that when Grignard and "cis-enone" are allowed to react in 1:1 ratio no isomerized "enone" is ever detected. It is apparent that the "trans-enone" formed by isomerization reacts with the Grignard reagent as soon as isomerization occurs. There is never any chance for the "trans-enone" to build up as in the reactions utilizing excess "enone". This difference in rate emphasises the point that there are two spearate pathways involved in the reaction of "CH_3MgBr" with "cis-enone". It is possible, but not necessary that these pathways involve different mechanisms (e.g., 1,2-cis-addition via polar pathway; 1,4- and 1,2-trans-addition via SET).

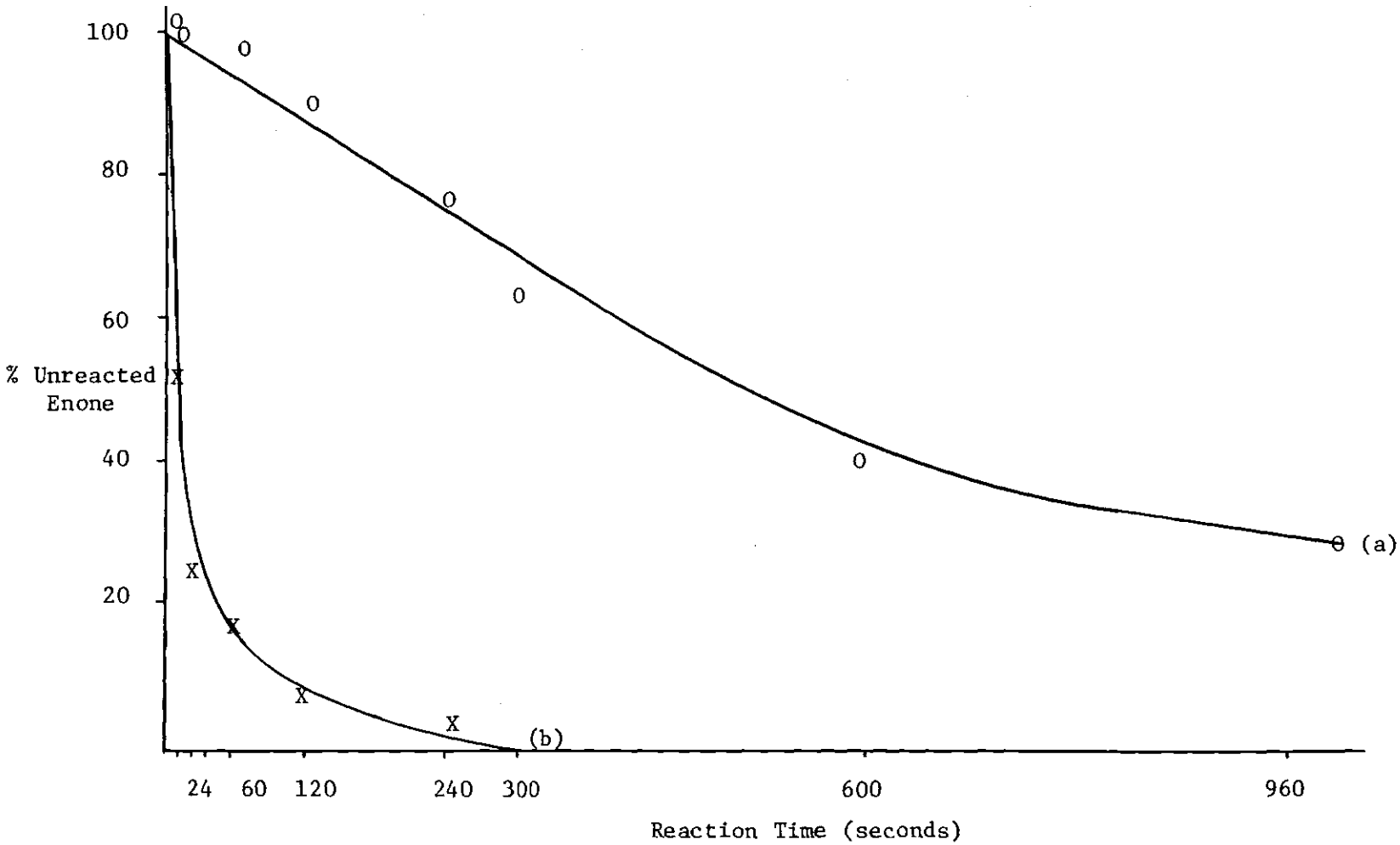


Figure 5. (a) Reaction of "CH_3MgBr" (0.0250 M) With "cis-enone" (0.0250 M) in Diethylether at Room Temperature. (b) Reaction of "CH_3MgBr" (0.0250 M) With "trans-enone" (0.0250 M) in Diethylether at Room Temperature.

Reactions of Other Organometallic Compounds with "cis-Enone

The reactions of MeLi with "cis- and trans-enone" (Table 28, entries 1-3) gave much the same results as the reactions of "allyl MgBr". The only product observed was 1,2-addition and little isomerization was observed in the absence of $FeCl_3$. It is interesting to note (entry 4) that MeLi reacts at a similar rate with both the "cis" and the "trans-enone". In this reaction an 87:13 mixture of cis:trans-enone is converted to an 82:18 mixture of cis:trans-1,2-addition products leaving a 89:11 mixture of starting materials. The MeLi apparently reacts about 1.4 times faster with the "trans"-enone than with the "cis"-enone. The real significance of these reactions lies in the observation that MeLi does not cause isomerization in the reaction with "cis-enone". As with the allyl Grignard reagents, the conclusion is that the reaction of MeLi with "cis-enone" is either polar or that the SET reaction proceeds to products too quickly for isomerization of an intermediate ketyl to be observed.

The reactions of $LiCuMe_2$ with the "enones" (Table 28, entries 5-7) all show complete isomerization of the starting enone and only 1,4-addition. This had been previously shown.[55] The reactions of $LiCu_2Me_3$[56] gave similar results (entries 10 and 11). The total isomerization of the starting "cis-enone" is, of course, indicative of SET. The reaction of "cuprates" with enones is thought to proceed through a SET pathway. The mixture of 4 equivalents of MeLi with 1 equivalent of CuI in THF has been shown to give an equilibrium mixture of $Li_2CuMe_3 \rightleftharpoons LiCuMe_2 + MeLi$.[56] The reaction of this reagent with "cis-enone"

(entry 8) gives 31.3% 1,4-addition and 68.6% 1,2-addition. Although almost all of the starting "cis-enone" is isomerized during the reaction, 85.3% of the 1,2-addition product is cis. Under these reaction conditions, it seems that the MeLi in the equilibrium mixture is reacting rapidly to give 1,2-addition (predominantly cis in the early stages). The Li_2CuMe_3 and the $LiCuMe_2$ are probably reacting more slowly through a SET pathway to yield 1,4-addition product and isomerized "enone". The 1,2-trans-addition product then could come about by reaction of MeLi with the isomerized "enone". These results may also be taken to indicate that the reaction of MeLi with "cis-enone" to form 1,2-addition product is faster than isomerization of the "enone" (electron transfer of $LiCuMe_2$ to the "enone").

The reactions of t-butyllithium with "cis- and trans-enone" provide more interesting results (Table 28, entries 12-14). With excess "cis-enone", t-butyllithium gives mostly (85.6%) unisomerized 1,2-addition product (possibly indicative of polar addition). However, this reaction also yields 1,4- (7.0%) and 1,2-trans-addition (6.8%) as well as 36.8% isomerization of the starting "cis-enone". This may be more indicative of a SET reaction which proceeds to products somewhat more rapidly than the rate of isomerization of "cis- to trans-ketyl", but not so much more quickly that no isomerization could occur. The addition of 40,000 ppm $FeCl_3$ causes a somewhat greater amount of isomerization of the remaining "enone", but slightly less isomerization of the products. This probably indicates no effect of iron on the main reaction pathway. (The iron, however, probably is involved in

the isomerization of the "enone" via route (B), equation 37). The significant result, once again, is seen in the reaction with the "trans-enone". The only products are 1,4- and 1,2-trans-addition, but more importantly, the ratio of % 1,4-addition:% 1,2-trans-addition (about 47:53) once again turns out to be the same starting with either the "cis- or trans-enone" regardless of how much 1,2-cis-addition product is produced in the reaction. In this reaction, the observation is dramatic because 1,2-cis-addition is the predominant product in the reaction with "cis-enone" and is not observed at all in the reaction with "trans-enone". Apparently (as in equation 37) again two pathways are involved: the reaction of t-butyllithium with "cis-enone" to produce 1,2-cis-addition product and the reaction of t-butyllithium with "trans-enone" to produce an approximately 47:53 mixture of 1,4- and 1,2-trans-addition products.

The reaction of Me_2Mg with "cis- and trans-enones" gives results very similar to those observed with t-butyllithium (except for the effect of iron on the reaction)(Table 29, entries 1-3). The reaction with "cis-enone" gives mostly 1,2-cis-addition with a small amount of 1,4- and 1,2-trans-addition. Very little isomerization of the starting enone is observed. The same reaction in the presence of 40,000 ppm $FeCl_3$ gives predominantly 1,4- and 1,2-trans-addition, but with only about 25% isomerization of the remaining "cis-enone". This probably indicates that Me_2Mg reacts much more rapidly with the "trans-enone" than with the cis-isomer as was observed in the case of "CH_3MgBr". The reaction of Me_2Mg with "trans-enone" shows only 1,4- and 1,2-trans-

addition. As noted with the "CH_3MgBr" and the t-butyllithium, the ratio of % 1,4-addition:1,2-trans-addition (about 49/57) remains nearly constant throughout these reactions, in spite of the dramatic change in 1,2-cis-addition produced. Again, the suggestion is that in the reaction with "cis-enone", 1,2-trans- and 1,4-addition products result from Me_2Mg addition to the "trans-enone" after isomerization (eq. 37).

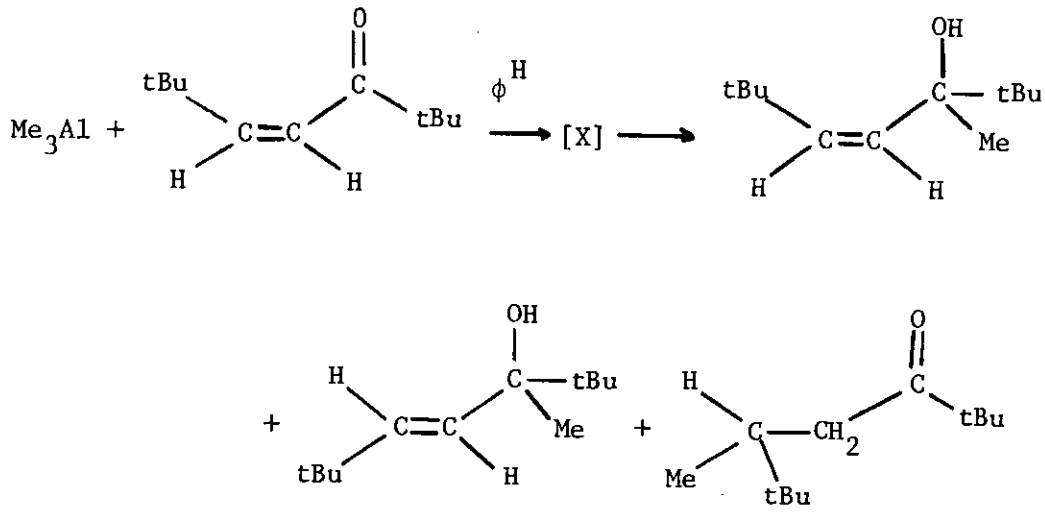
The reactions of various organoaluminum and zinc compounds with "cis- and trans-enone" were studied in diethylether and benzene. Much less reaction was observed with these compounds than with the corresponding magnesium compounds. When Me_3Al was allowed to react with "cis-enone" for 46 hours in diethyl ether (Table 29, entry 4), almost no reaction occurred; the only product observed was a trace amount of 1,2-trans-addition. The same reaction with 40,000 ppm $FeCl_3$ added (entry 5) gave 17% reaction to yield a 15.3:84.7 ratio of 1,4-addition:1,2-trans-addition as well as 27% isomerization of the starting "cis-enone". It appears that the Me_3Al is unable to react with the "cis-enone" but in the presence of $FeCl_3$ some isomerization of the "enone" takes place. Reaction of this isomerized "enone" with Me_3Al then leads to the mixture of 1,4- and 1,2-trans-addition. It is apparent by comparison of entries 6 and 7, however, that the rate of reaction of Me_3Al with "trans-enone" is not affected by the presence of $FeCl_3$. Both the reaction of Me_3Al with "trans-enone" in ether, and the same reaction in the presence of 40,000 ppm $FeCl_3$ show the same amount of reaction ($\sim$45%) after 46 hours at room temperature. The product distribution is slightly affected by the $FeCl_3$; somewhat more 1,4-

-addition is seen in the presence of $FeCl_3$. That there are two distinct pathways involved in this reaction (as in eq. 27) is quite obvious, since the Me_3Al reacts with the "trans-enone" to generate 1,4- and 1,2-trans-addition products, but does not even react with the "cis-enone".

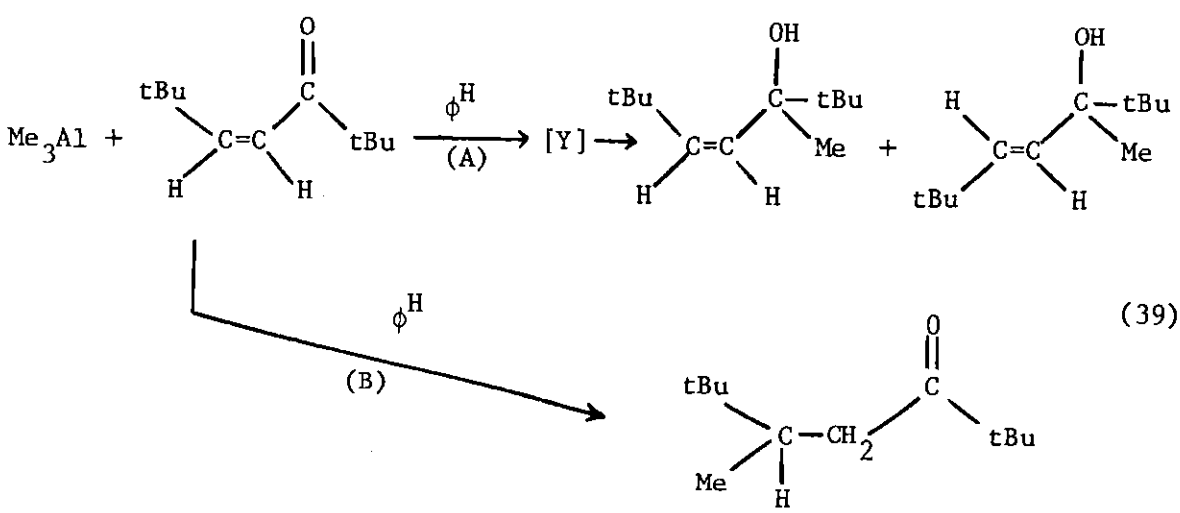
The reaction of Me_3Al with "cis- and trans-enones" in benzene, however, is a different matter entirely. When Me_3Al was allowed to react with "cis-enone" in benzene for 44 hours, almost 50% reaction occured (Table 29, entry 8). The product mixture includes 28.5% 1,4-addition, 38.5% 1,2-trans-addition and 33.1% 1,2-cis-addition. Considerable isomerization of the starting "cis-enone" was also observed. The same reaction in the presence of 40,000 ppm $FeCl_3$ (entry 8) showed a marked increase in the amount of 1,4-addition observed, as well as an increase in the percent isomerization of both the 1,2-addition product and the starting "cis-enone". It appears in this case that iron catalyzes the formation of 1,4-addition product, possibly via a SET pathway. The reaction of Me_3Al with "trans-enone" (entry 10) in benzene gives about 60% conversion to a mixture containing 29.4% 1,4-addition and 70.6% 1,2-trans-addition. Addition of 40,000 ppm $FeCl_3$ under these conditions has little effect on the reaction. (The % 1,4-addition product increases by about 5% and the % conversion increases to about 77%, but these changes are not so significant.) A comparison of entries 8 and 10, however, shows a significant change from the trend observed in diethylether. The amount of 1,4-addition observed in the reaction of Me_3Al with "cis-enone" and that observed in the reaction

with "trans-enone" is the same when the solvent is benzene. The reaction with "cis-enone" gives a mixture of cis- and trans-1,2-addition while the reaction with "trans-enone" gives only trans-1,2-addition, but in each case the relative percent 1,2-addition is the same. This is not at all indicative of the 2-pathway reaction indicated in equation 37. The data is much more consistant with a mechanism involving a single pathway leading to all products (such as equation 38) or a pair of pathways (such as equation 39) in which one pathway leads to 1,4-addition (path A) and the other leads to both cis- and trans-1,2-addition (path B). It is probable that either mechanism would have to involve some intermediate ([X] or [Y]) in which the "enone" was capable of isomerization. It is clear, in any event, that the mechanism of this reaction in benzene is different than the one in diethylether and is different from those proposed to involve the two pathways enumerated in equation 37. It is difficult to make any statements concerning the polar of SET nature of these reactions in ether or in benzene based on this limited amount of data. The slow reaction rates and the general lack of effect of $FeCl_3$ on the reactions tends to indicate that the reactions are polar. The large amounts of isomerization indicate SET. Competing polar and SET mechanisms also seem possible.

The reaction of Me_2AlCl with "cis-enone" for 44 hours in benzene gives only 8% conversion to a mixture containing 48.8% 1,4-addition, 41.5% 1,2-trans-addition and 9.8% 1,2-cis-addition. All of the "enone" that remains, however, is isomerized to the trans-isomer.



(38)

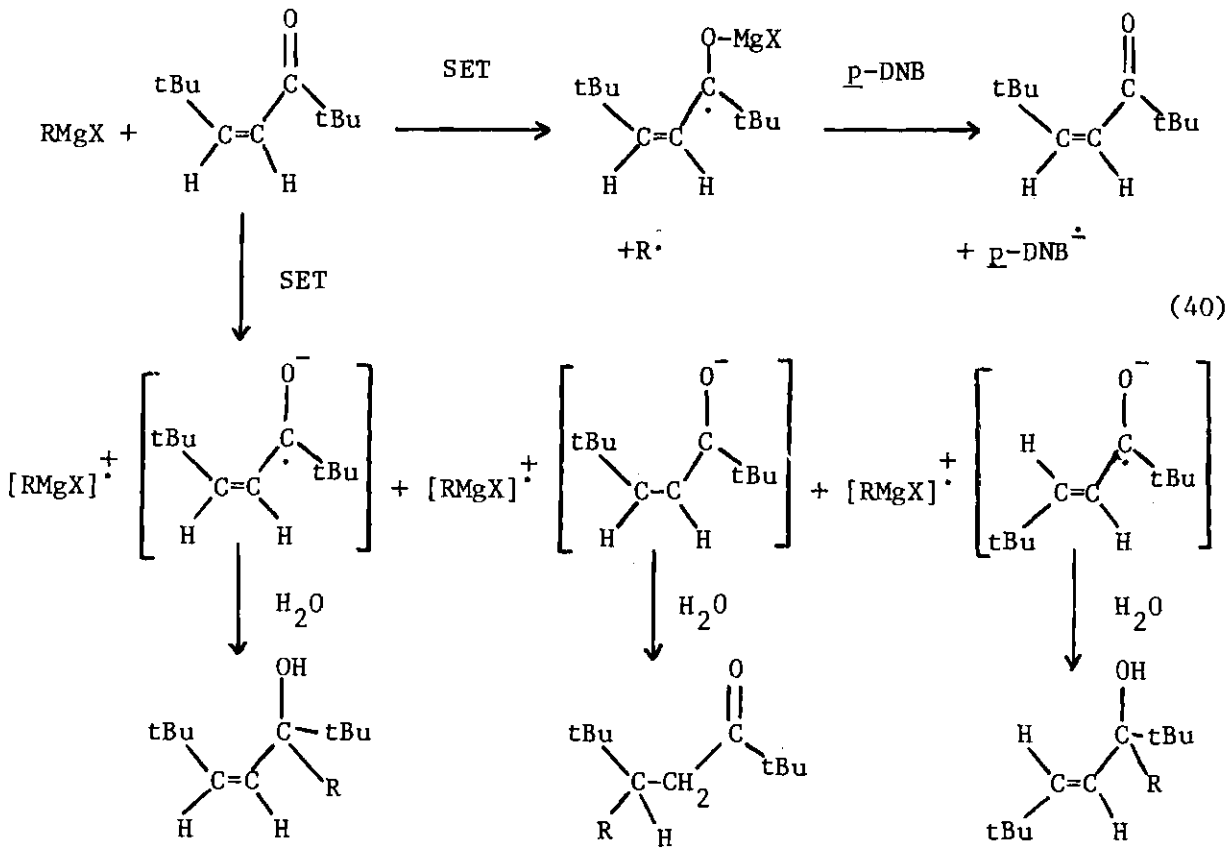


(39)

The same reaction in the presence of 40,000 ppm $FeCl_3$ yields 5% conversion to a mixture that is 58.3% 1,4-addition product and 41.7% 1,2-trans-addition product. The reagents Me_2Zn, "MeZnBr" and t-Bu_2Zn all failed to give any reaction with either "cis- or trans-enone" in the presence or absence of 40,000 ppm $FeCl_3$ after 44 hours of contact in benzene or 46 hours of contact in diethylether at room temperature. None of these reactions even isomerized the starting material. The lack of reactivity of these reagents makes conclusions concerning mechanistic pathways impossible.

Effect of p-DNB on "Enone" Reactions

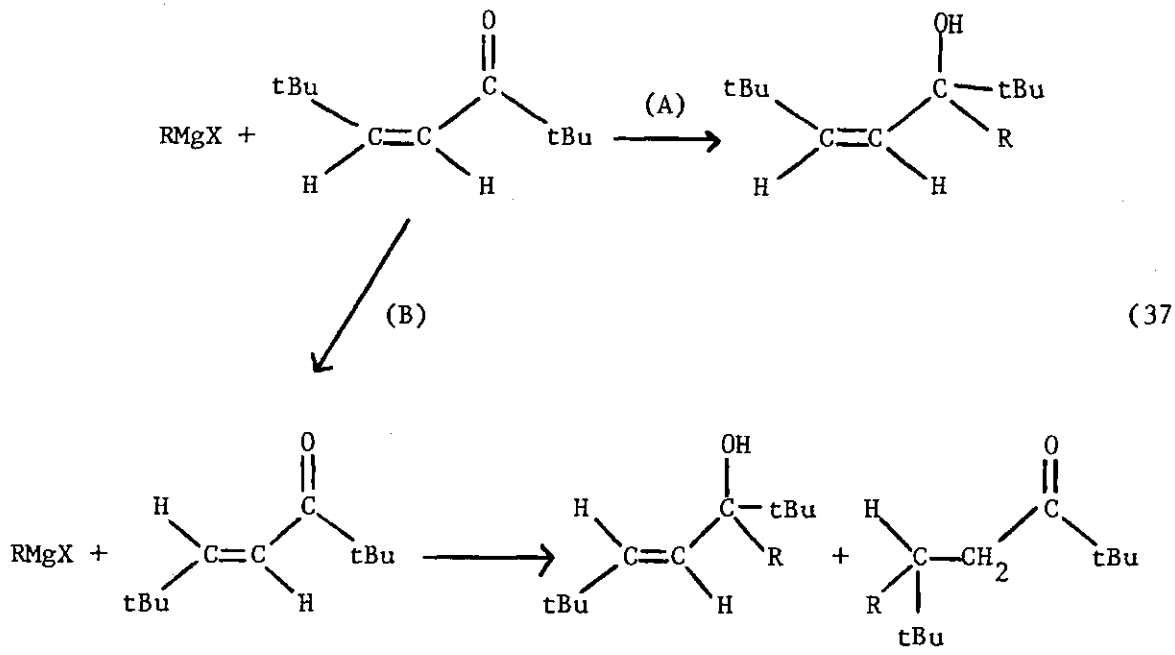
The reaction of "CH_3MgBr" with "cis-enone" in the presence of 20% p-DNB (Table 30, entry 1) shows about the same product mixture as the reaction in the absence of p-DNB (Table 29, entry 4), however, without the isomerization of the starting "cis-enone" observed in that reaction. This is the best single piece of data supporting the case for a SET mechanism for the reaction of "CH_3MgBr" with ketones. If the p-DNB is indeed able to eliminate isomerization of the "cis-enone" by removing an electron at a faster rate than "cis- to trans-ketyl" isomerization (see equation 36), the isomerized addition products could then come about only through a SET process in the product formation step of the mechanism. It is conceivable that the p-DNB could intercept the radical from the formation of a "free" ketyl radical anion, and yet be unable to do the same in the case of a bound radical anion-radical cation pair. Possibly, then, isomerization of the starting "cis-enone" is occurring exclusively through a process involving the



(40)

free ketyl; a process that could be stopped by p-DNB incorporation in the reaction. SET formation of radical anion-radical cation pairs involving Grignard reagent and "enones" which would presumably be unaffected by the p-DNB could then collapse to form the observed addition products (eq. 40).

It is more likely, though, that the Grignard reaction with the "enone" involves the two pathways postulated in equation 37 (repeated here). It is likely that the isomerization step (path B) involves SET to give the "free" ketyl and that p-DNB reverses this step by interception of the ketyl radical anion to regenerate the "cis-enone" before much isomerization can take place. The reaction of "CH_3MgBr" with "cis-enone"



(37)

in the presence of 30% p-DNB (Table 30, entry 4) shows that the more p-DNB present in the reaction, the less isomerization occurs. While this result is not irreconcilably inconsistant with the mechanism proposed in equation (40), it certainly seems to be more consistent with the one proposed in equation (37). The role of the p-DNB apparently is only to inhibit isomerization of the "cis-enone". It appears, from the trend observed in Table 30 entries 1 and 4 that in the (hypothetical) reaction of "CH_3MgBr" with "cis-enone" where enough p-DNB has been added such that no isomerization of the "enone" would occur, the only product would be 1,2-cis-addition. Unfortunately, it is impossible to test this hypothesis (other than by extropolation of these results) because larger concentrations of p-DNB destroy all of the "CH_3MgBr" in a side reaction and no reaction with the "cis-enone" is observed. This trend, however,

does seem to enhance the argument that the reaction of methyl Grignard reagents with ketones proceeds (at least predominantly) through a polar mechanism (in the absence of transition metal impurities). The alternate argument that the 1,2-cis-addition product is the result of addition to the "cis-enone" via a SET pathway too rapid for the reaction to be "short-circuited" by the p-DNB is not refutable, however.

Table 30, entries 6-8, show that the reaction of "t-BuMgCl" with "cis-enone" is not significantly affected by p-DNB, except for the distruction of the Grignard reagent in a side reaction which renders it useless for reactions with the enone. "Allyl MgBr" reactions with "cis-enone" (entries 9 and 10) are entirely unaffected by p-DNB. Presumably this Grignard reagent reacts with a ketone faster than it does with the p-DNB. This, in itself, points to a polar reaction pathway, since the reduction potential of p-DNB is much lower than that of "cis-enone" and a SET reaction would be expected to occur predominantly with the substrate of lower reduction potential. (The reduction potentials are: "cis-enone:, -2.21 V;[57] "trans-enone", - 2.22 V;[52] and p-DNB, - 0.54 V;[51] all versus SCE in DMF.) The reactions of $LiCuMe_2$ with "trans- enone" in the presence of p-DNB (entries 11 and 12) like those of "t-BuMgCl" are only affected to the extent that the cuprate reacts with the p-DNB in a side reaction which prevents addition to the enone.

CHAPTER IV

CONCLUSION

The mechanism of Grignard reactions with ketones is dependent on a variety of factors. The nature of the alkyl group in the Grignard reagent is of utmost importance. It is probably the most important single factor involved in determining the extent of SET to be observed in the reaction with a given ketone. The purity of the magnesium used to prepare the Grignard reagent as well as the method of Grignard preparation has been shown to dramatically affect the reactions with ketones. The reduction potential of the ketone and the nature of the solvent in which the reaction is carried out are also important factors determining the mechanistic pathway to be involved in Grignard reactions with ketones. It is apparent that reactions of "t-BuMgCl" with benzophenone, fluorenone, and probably "cis-enone" proceed via a SET pathway while the reaction of "t-BuMgCl" with acetone seems polar. The "iron intermediate" proposed to result from the reaction of "CH_3MgBr" with trace amounts of $FeCl_3$ apparently reacts via SET with benzophenone and fluorenone to yield pinacol; probably reacts with "cis-enone" to give isomerization; yet is apparently unable to transfer an electron to a ketone with a reduction potential as high as acetone. In reactions where SET is obviously occurring, (such as the reaction of "CH_3MgBr" with benzophenone in the presence of $FeCl_3$ to give a large amount of pinacol), shift to a more polar solvent (e.g., from diethylether to THF) results in an observable

increase in the proportion of SET products (e.g. pinacol).

The mechanism (Chapter I, Scheme (1)) initially suggested by Blombert-Mosher and Fauvarque for the reaction of Grignard reagents with ketones remains reasonably valid. However, the question of whether the 1,2-addition product in Grignard reactions with ketones is formed through a polar pathway, a SET pathway, or a combination of the two, is complex and is not completely answered by this thesis. Other members of our team of investigators are still working on the solution to this problem.

The formation of pinacol in the reaction of "CH_3MgBr" with benzophenones has been shown to be the result of a transition metal catalyzed SET reaction. Iron and other first row transition metals appear to be the best catalysts. The isolation of erythro and threo pinacols in addition to equilibrium studies relating rates of formation of the two isomers show that although iron salts catalyze electron transfer to form the ketyl, iron is not involved in the formation of the pinacolates.

The formation of "CH_3MgBr" from magnesium and methyl bromide in ether has been shown to be accompanied by the formation of about 0.2% of a very reactive magnesium hydride species. This hydride has been shown to be responsible for the formation of benzhydrol in reactions of benzophenones using a large excess of "CH_3MgBr". Excess methyl bromide has been shown to destroy the activity of this hydride.

The reactions of tert-butylmagnesium chloride with benzophenones, fluorenone, and cis- and trans-2,2,6,6-tetramethylhept-4-ene-3-one

apparently occur via a SET pathway involving a radical anion-radical cation pair (after SET) which can collapse to give addition products or diffuse to give pinacol and isobutane (eq. 28). The reaction of "t-BuMgCl" with $FeCl_3$ apparently produces an iron hydride species which is capable of reducing acetone (more quickly than Grignard addition to acetone) and "enone" (less quickly than Grignard addition to the "enone") but which does not react with benzophenones or fluorenone in the presence of the Grignard reagent.

The reactions of allyl Grignard reagents with ketones are very rapid and give indications of only a polar mechanism, however, a SET pathway in which the addition step very rapidly follows the electron transfer step cannot be ruled out. "Allyl-MgBr" does not seem to be affected by reaction with $FeCl_3$.

The reactions of methyl Grignard reagents with ketones are not easily interpreted in terms of the nature of alkyl transfer. They show some of the characteristics of both polar and SET reactions. The main complicating factor is that the reaction of "CH_3MgBr" with $FeCl_3$ (even in trace amounts) produces a species which is capable of SET to each of the ketones tested, except acetone, by an apparently catalytic process involving the Grignard reagent. This electron transfer leads to pinacol in the case of benzophenone or fluorenone, and isomerization in the case of "cis-enone". If the mechanism of methyl Grignard reactions with ketones does involve SET in the absence of transition metal catalysis to give a radical anion-radical cation pair, collapse of this pair to 1,2-addition product must be extremely rapid and

exclusive. No 1,6-addition product or pinacol is ever observed via this pathway.

Grignard reagents have been shown to react with p-dinitrobenzene. However, small amounts of p-DNB in Grignard reactions with ketones have been shown to be capable of inhibiting the formation of "free ketyls" in the solution. Grignard reactions in the presence of p-DNB produce no pinacol in experimental conditions under which it would normally be a product and show reduced amounts of isomerization with "cis-enone".

The primary matter of concern not answered by this thesis is the question of the nature of the alkyl transfer step in Grignard reactions with ketones. In the next few pages I would like to speculate somewhat on this matter. Radical stabilities increase generally in the order:

$$CH_3\cdot < CH_3CH_2\cdot < (CH_3)_2CH\cdot < (CH_3)_3C\cdot < CH_2{=}CH{-}CH_2\cdot$$ [58]

while carbanion stabilities increase generally in the order:

$$(CH_3)_3C^{\ominus} < (CH_3)_2CH^{\ominus} < CH_3CH_2^{\ominus} < CH_3^{\ominus} < CH_2{=}CH{-}CH_2^{\ominus}$$ [59]

It may be expected that Grignard reagents with alkyl groups which form more stable carbanions than radicals should react via a polar pathway while those which form more stable radicals than carbanions may be expected to react via SET. This should, then, lead to a scale of

Grignard reactivities (with a given ketone) which may be marked Polar on one end and SET on the other.

POLAR ——————————————————————————SET

Most Grignard reagents, though, would be likely to fall between those two extremes. The middle region, of course, is just the region in which interpretations with respect to the nature of the alkyl transfer step are most difficult. It is apparent that t-butyl Grignard reagents lie near the SET side of the scale, as would have been anticipated based on the stability of t-butyl radicals and the instability of t-butyl carbanions. It is clear, as well, that methyl Grignard reagents lie further toward the Polar side of the scale, though exactly how close to the Polar end is difficult to estimate. This is also in keeping with the stability of methyl carbanions and the instability of methyl radicals. Reagents such as "allyl-MgBr" are difficult to place on the scale even intuitively since both allyl carbanions and allyl radicals are quite stable.

An attempt has been made in this thesis and in work carried out by other members of this research group to develop a probe system which would rearrange or otherwise isomerize on a time scale more rapid than the Grignard reaction with the ketone. Probes of this sort have an intrinsic disadvantage. While isomerization may indicate SET, lack of isomerization does not indicate that reaction is polar. It may indicate only that the probe is not quick enough to detect SET. With this in

mind, other methods of distinguishing SET from polar reactions are being investigated. It seems that SET reaction rates should vary with the stabilities of the corresponding alkyl group radicals (of the Grignard reagents) and should not be strongly affected by steric bulk. On the other hand, polar reaction rates should vary with the stabilities of the corresponding carbanions, and should be more affected by steric bulk. Preliminary results of a study carried out by Daniel Campbell[44] show the relative rates of Grignard reactions with benzophenone and 2-MBP:

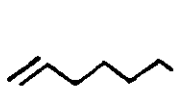
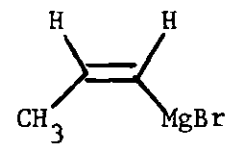
	RELATIVE RATE OF ALKYLATION OF		
R-Group of Grignard	$Ph_2C{=}O$	2-MBP	$k_{Ph_2CO}/k_{2\text{-MBP}}$
iso-butyl	10.7	0.4	29.7
methyl	26.0	1.0	26.0
ethyl	562	22.3	25.0
n-hexyl	481	22.5	21.4
iso-propyl	2639	58.0	45.5
tert-butyl	2587	1797	1.4
allyl	7190	31454	0.23
crotyl	130000	200000	0.65

The relative rates vary in the same direction as the radical stabilities, which may be taken as an indication of SET mechanism. While the first four Grignard reagents on the list show signs of being affected by the steric bulk (slower reactions with 2-MBP than with benzophenone), the last three Grignard reagents do not. This must surely be taken as a sign of a SET pathway in the case of t-butyl, allyl, and crotyl

Grignard reagents. On the other hand, preliminary results show that the rate of reaction between "t-BuMgCl" and di-tert-butyl ketone is considerably slower than the reaction between "CH_3MgBr" and that ketone. This is a rate difference in the direction predicted by carbanion stabilities and may be taken as evidence of polar addition to this ketone. Further work is being carried out in this area.

At the present time the following statements concerning the alkyl transfer step in Grignard reactions with ketones can be made:

1. If the reduction potential of the ketone is low enough, alkyl transfer can occur via a SET pathway (e.g. "t-BuMgCl" reactions with benzophenone).

2. If a radical probe is placed in the R-group of the Grignard reagent (e.g.  or ), no cyclization or isomerization has ever been observed in the 1,2-adduct to benzophenone.

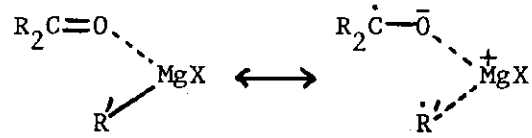
3. Relative rates of Grignard reactions with benzophenone vary according to the corresponding relative radical stabilities.

4. Grignard reagent with alkyl groups which have low relative radical stabilities show more sensitivity to steric bulk than those with alkyl groups which easily stabilize radicals.

5. If the reduction potential of the ketone is too high, no obvious SET products are observed in Grignard reactions.

6. Relative rates of Grignard reactions with acetone and with di-tert-butyl ketone vary according to the corresponding carbanion stabilities.

While it is possible to imagine a theory to describe each case, it seems that the best description would be one which can account for all of the products in each case. The overall mechanism described in equation 29 provides such a description. The reaction would be polar if the reduction potential of the ketone is too high for a radical cation-radical anion pair to be formed (through SET). For ketones of appropriate reduction potential, electron transfer to give the radical cation-radical anion pair would occur.



This pair may be thought of as a charge transfer complex originating from the σ-complex. The tightness or looseness of the complex would undoubtedly be affected by the stability of the incipient radical, R'·. A tight complex, of course, would feel the effect of steric bulk near the reaction site much more than would a loose complex. This accounts for the relative reactivities of various Grignard reagents as well as the effect of steric bulk (which is observed only with some Grignard reagents). A tighter complex may be expected to give only 1,2-addition product if the R-group is never free enough to move from the immediate reaction site (thus methyl Grignard reactions could be proceeding via this SET mechanism even when 1,2-addition is the only product observed). A loose complex, on the other hand, may be expected to give 1,4- and 1,6-addition products as well as some complete

dissociation of R$^{\cdot}$ to give R-H + pinacol. This accounts for the differences in product distribution in reactions of various Grignard reagents with benzophenone. The final point to be made concerning this mechanism for Grignard reactions with ketones is that the alkyl "radical" in this description is never completely "free" (except upon dissociation to give pinacol and R-H). This explains the observation that no isomerization or cyclization ever occurs in the experiments where radical probes were placed in the R-group of the Grignard reagent. This mechanism is able to explain all that is presently known about the alkyl transfer step in Grignard reactions with ketones. In addition, it is apparent that pinacol-type products can come about by dissociation of the radical cation-radical anion pair (t-butyl Grignards) or via a transition metal catalyzed side reaction that is unrelated to the main reaction pathway (methyl Grignards) depending on the R-group of the Grignard reagent and the stabilities of the intermediate alkyl transition metal compounds. Reduction products can come about via β-hydrogen reduction pathways, or, even in the absence of β-hydrogen atoms, may occur due to small amounts of -MgH species which has been shown to be formed in the Grignard formation reaction.

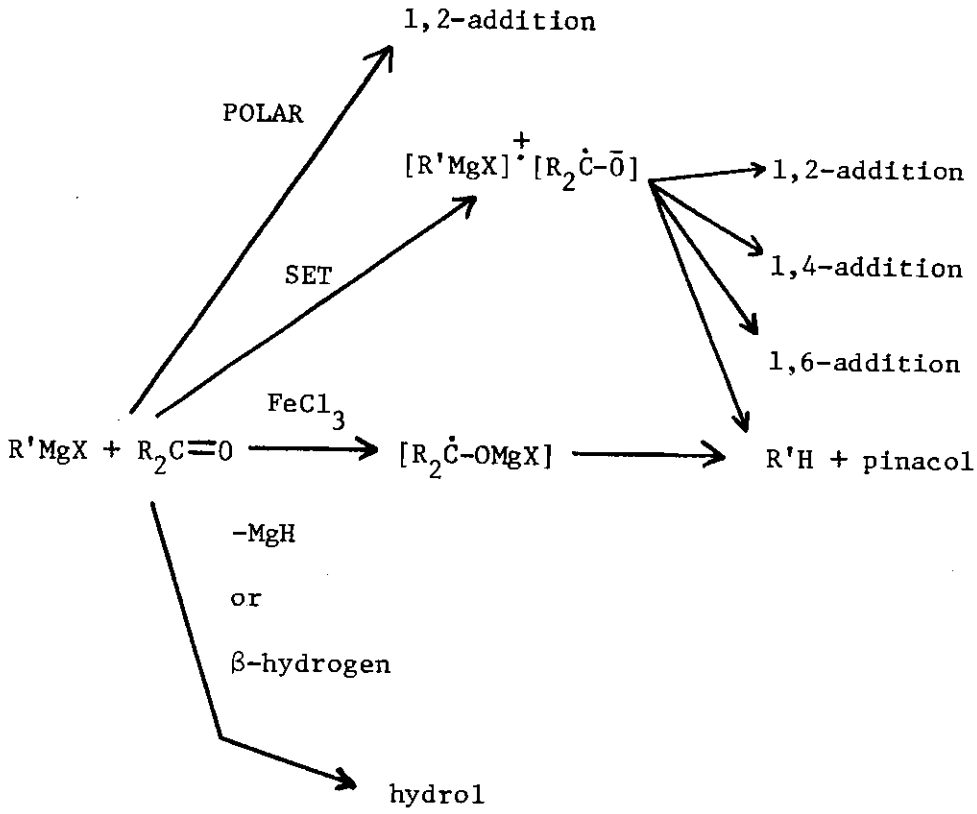

1,2-addition
POLAR
[R'MgX]$^{+}$ [R$_2$Ċ-Ō]
1,2-addition
1,4-addition
1,6-addition
SET
FeCl$_3$
R'MgX + R$_2$C=O
[R$_2$Ċ-OMgX]
R'H + pinacol
-MgH
or
β-hydrogen
hydrol

Table 1. Products From the Reaction of Methylmagnesium Bromide (1.50 M) With 2-Methylbenzophenone (0.0375 M) in Diethyl Ether at Room Temperature. Effect of Magnesium Purity at 400:1 Grignard to Ketone Ratio.

		Yield %				Elemental Analysis[e] (ppm)											
Grade of Mg	Grignard Prepared In Excess	1,2-Addn.[a]	Pinacol[b]	Hydrol[c]	Other[d]	Ti	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ag	Pb	Na	K
Single Crystal	Mg	68	10	13	9	0	0	70	18	0	0.1	3	48	140	0	0.3	0.4
Dow No. 5	Mg	71	7	13	8	17	0	6	18	0	1.0	6	20	0	0	0.3	0.4
Ventron Chips	Mg	77	14	0	10	0	0	21	22	0.3	0	0.1	56	0	0	0.3	0
D. S.[f]	Mg	62	2	36	0	0	0	0	0.1	0	0	0.1	25	0	0	9	0.9
ROC/RIC	Mg	92	1	4	3	0	0	7	10	0	0	0	73	0	18	0	1
T. S.[f]	Mg	41	1	58	0	0	0	0	0	0.3	0	0	27	0	0	18	16
GGT[f]	Mg	55	19	8	19	0	0	130	140	0	0.1	3	54	0	0	0.3	0
Ventron Chips	CH_3Br	85	10	0	5	0	0	21	22	0.3	0	0.1	56	0	0	0.3	0
ROC/RIC	CH_3Br	94	4	0	2	0	0	7	10	0	0	0	73	0	18	0	1
T. S.[f]	CH_3Br	82	2	4	3	0	0	0	0	0.3	0	0	27	0	0	18	16

a. 1-phenyl-1(2-methylphenyl) ethanol. b. 2,2'-dimethylbenzopinacol. c. 2-methylbenzhydrol. d. apparently 1-(2,6-dimethylphenyl)-1-phenylethanol. e. Analysis by Microtrace Analytical Services, Industry, CA 91746.

f. Key: DS = Dow Doubly Sublimed; TS = Dow Triply Sublimed; GGT = Baker, Grignard Grade Turnings.

Table 2. Products From the Reaction of Methylmagnesium Bromide with Benzophenone

Exp.	Magnesium Purity[a]	Grignard Prepared in	Solvent	Grignard Conc.	G/K Ratio	% 1,2-Addition	% Benzopinacol	% Benzhydrol	ppm $FeCl_3$ Catalyst
1	GGT	xs Mg	Ether	0.178 M	1.42	98.0	2.0	0	
2	SC	xs CH_3Br	Ether	0.213 M	1.17	>99.4	0.6	0	
3	GGT	xs Mg	Ether	1.38 M	125	90.6	9.4	0	
4	SC	xs CH_3Br	Ether	0.048 M	0.05	>99.2	0.8	0	
5	SC	xs CH_3Br	Ether	0.188 M	1.5	99.0	1.0	0	4
6	SC	xs CH_3Br	Ether	0.188 M	1.5	97.4	2.6	0	40
7	SC	xs CH_3Br	Ether	0.188 M	1.5	81.3	18.7	0	400
8	SC	xs CH_3Br	Ether	0.188 M	1.5	54.0	46.0	0	4000
9	SC	xs CH_3Br	Ether	0.188 M	1.5	29.5	70.5	0	40,000
10	GGT	xs Mg	Ether	0.188 M	1.5	27.5	72.5	0	40,000
11	SC	xs CH_3Br	THF	0.188 M	1.5	99.2	0.8	0	
12	SC	xs CH_3Br	THF	0.188 M	1.5	27.0	72.0	<1.0	4000
13	SC	xs CH_3Br	HMPA	0.187 M	1.5	96.6	0.8	2.6	4000
14	SC	xs CH_3Br	HMPA	0.187 M	1.5	95.2	0.8	4.0	

[a]key: GGT = Grignard Grade Turnings; SC = Single Crystal; G = Grignard; K = Ketone

Table 3. Products From the Reaction of t-Butylmagnesium Chloride With Benzophenone

Exp.	Magnesium Purity[a]	Grignard Prepared In	Solvent	Grignard Conc.	G/K[b] Ratio	% 1,6-Addition	% 1,2-Addition	% Benzopinacol
15	SC	xs t-BuCl	Ether	0.188 M	1.5	48.0	42.3	9.7
16	GGT	xs Mg	Ether	0.188 M	1.5	50.0	40.3	9.7
17	GGT	xs Mg	Ether	0.188 M	20	48.5	40.7	10.8
18	GGT	xs Mg	Ether	0.230 M	121	50.0	42.2	8.8
19	SC	xs t-BuCl	Ether	0.033 M	0.05	43.8	31.2	25.0
20	GGT	xs Mg[c]	Ether	0.188 M	1.5	49.1	38.2	12.7
21	SC	xs t-BuCl	THF	0.208 M	1.68	41.3	47.0	11.7
22	SC	xs t-BuCl[d]	THF	0.188 M	1.5	47.4	45.3	7.3
23	SC	xs t-BuCl	HMPA	0.188 M	1.5	26.0	72.3	<1.7
24	SC	xs t-BuCl[e]	HMPA	0.188 M	1.5	20.8	77.8	<1.4

a. Key: GGT = Grignard Grade Turnings; SC = Ventron, Single Crystal. b. G = Grignard; K = Ketone. c. 400 ppm $FeCl_3$. d. 4000 ppm $FeCl_3$ added. e. 2,500 ppm $FeCl_3$, $CoCl_2$, CuCl and $CrCl_3$ added.

Table 4. Products From the Reaction of "CH_3MgBr"[a] (0.188 M) With Benzophenone (0.412 M) Doped with 4000 ppm $FeCl_3$ in Diethylether at Room Temperature in the Presence of Various Amounts of HMPA.

Exp.	HMPA (mmoles)	HMPA/G	% Pinacol[b]	% 1,2-Addition
1[c]	0	0	<0.6	99+
2[c]	0.17	0.184	<0.4	99+
3[c]	2.29	2.44	<1.0	99+
4	0	0	46.0	54.0
5	0.10	0.106	29.8	70.2
6	0.24	0.25	17.8	82.2
7	1.07	1.14	15.6	84.4
8[d]	1.07	1.14	15.1	84.9
9	2.17	2.31	<0.6	99+
10	2.45	2.61	<1.0	99+
11	5.09	5.42	<0.4	99+

a. Made from Single Crystal Magnesium with excess CH_3Br.

b. Normalized: 100% = % Pinacol + % Hydrol + % Addition.

c. No $FeCl_3$

d. Inverse Addition (Ketone last)

Table 5. Effect of Added Transition Metal Salts (0.5 mole %) in the Reaction of 1.5 mmole "CH_3MgBr"[a] and 1.0 mmole 2-Methylbenzophenone in Et_2O at Room Temperature.[b]

	% Yield		
Metal Salt	1,2-Addition[c]	Pinacol[d]	2-Methyl-benzhydrol
V $(acac)_3$[e]	95	5	0
Cr $(acac)_3$	81	19	0
Mn $(acac)_3$	81	19	0
$MnCl_3$	91	9	0
Fe $(acac)_2$	45	55	0
Fe $(acac)_3$	40	60	0
$FeCl_3$	38	62	0
Fe $(CO)_5$	56	44	0
Co $(acac)_3$	49	51	0
Co Cl_2	51	49	0
Ni $(acac)_2$	87	13	0

The salts of the following metals all yielded 100% 1,2-Addition: Sr, Y, La, Zr, Hf, Ce, Th, Mo, W, Ru, Rh, Pd, Pt, Cu, Ag, Zn, Cd, Al, Ga, In, Tl, Sn, Pb.

a. Prepared from doubly sublimed magnesium using excess magnesium. b. Analysis by NMR. c. 1-phenyl-1-(2-methylphenyl) ethanol. d. 2-2'-dimenthylbenzopinacol. e. acac = acetylacetonate.

Table 6. Formation of Products with Respect to Time in the Reaction of "CH_3MgBr"[a] (0.20 M) with 2-Methylbenzophenone (0.020 M) and $FeCl_3$ (0.05 mole %) in Et_2O at -30°.[b]

		% Yield				
			Pinacol[d]			
Rx Time	Unreacted Ketone (%)	1,2-Addition[c]	Erythro	Threo	2-Methyl-benzhydrol	By-Product/Addition[e]
40 min.	82 (91)[f]	7 (9)[f]	7	4	0	1.5
2 hrs.	47 (85)	21 (15)	19	13	0	1.5
3 hrs.	24 (77)	31 (23)	28	17	0	1.5
4 hrs.	16	31	37	16	0	1.4

a. Prepared from doubly sublimed magnesium using excess magnesium. b. Analysis by NMR. c. 1-phenyl-1-(2-methylphenyl) ethanol. d. 2,2'-dimethylbenzopinacol. Composed of both threo and erythro pinacols. e. (2-Methylbenzhydrol + Pinacol)/Addition Product. f. Numbers in parenthesis gives values for uncatalyzed reaction.

Table 7. Kinetic/Thermodynamic Pinacol Equilibrium in the Reaction of "CH_3MgBr" (.30 M) with 2-Methylbenzophenone (.025 M) in the Presence of 1.74 mole % $FeCl_3$ at -25°.

	% Pinacol[a]		
Time (hrs)	Kinetic	Thermodynamic	% Reaction[b]
∿.08	51.9	48.1	5.8
.33	51.1	48.9	32.1
1	51.0	49.0	77.1
3	50.0	50.0	85.9
9	45.4	54.6	86.8
24	35.0	65.0	87.9
48	27.3	72.7	90.0
120	28.1	71.9	98.1
241	14.6	85.4	99.3
532	5.1	94.9	100.0

a. Normalized as % kinetic + % thermodynamic pinacol = 100%. Each reaction contained 2-4% 1,2-addition product as the only other product.

b. 100% - ketone detected in product mixture.

Table 8. Kinetic/Thermodynamic Pinacol Equilibrium Reaction of a 36/64 Mixture of the Diastereomers with "CH_3MgBr" (.30 M) at -25°.

	% Pinacol[a]	
Time (hrs)	Kinetic	Thermodynamic
0	36.0	64.0
3	36.0	64.0
24	29.9	70.1
120	18.8	81.2
308	4.6	95.4
643	5.3	94.7

a. Normalized as % kinetic + % thermodynamic pinacol = 100%

Table 9. Kinetic vs. Thermodynamic Pinacol Equilibrium: Reaction of 97.5/2.5 Mixture of the Diastereomers (0.025 M) with "CH_3MgBr" (.30 M) at -25° with and without $FeCl_3$ (1.74 mole %).

		% Pinacol[a]	
Time (hrs)	% $FeCl_3$	Kinetic	Thermodynamic
0	0	2.5	97.5
0	1.74	2.5	97.5
1	0	5.1	94.9
1	1.74	5.1	94.9
4	0	5.0	95.0
4	1.74	5.1	94.9
8	0	5.0	95.0
8	1.74	5.1	94.9
24	0	5.0	95.0
24	1.74	4.9	95.1
48	0	4.8	95.1
48	1.74	5.0	95.0

a. Normalized as % kinetic + % thermodynamic pinacols = 100%

Table 10. Products of the Reaction of "CH_3MgBr" (0.188 M) with Benzophenone (0.125 M) in Diethylether at Room Temperature in the Presence of Large Quantities of $FeCl_3$ or $FeCl_2$ for 3 Hours.

Exp.	% $FeCl_3$	% $FeCl_2$	% $MgBr_2$	% Pinacol[a]	% 1,2-Addition[a]	% Conversion[b]
1	20	0	0	87.2	12.8	73.3
2	40	0	0	89.9	10.1	47.3
3	60	0	0	92.3	7.7	31.5
4	80	0	0	93.4	6.6	15.8
5	100	0	0	-	-	0
6	0	35	0	81.6	18.4	95.0
7	0	70	0	85.7	14.3	90.3
8	0	110	0	87.8	12.2	89.0
9	100	0	400[c]	87.5	12.5	36.0
10	100	0	225[d]	89.8	10.2	15.3

a. Normalized such that % Pinacol + % 1,2-Addition = 100%.

b. 100% - Unreacted Ketone.

c. Equivalent Mg/Fe ratio to Exp. No. 1, Fe equivalent to Exp. No. 5.

d. Equivalent Mg/Fe ratio to Exp. No. 2, Fe equivalent to Exp. No. 5.

Table 11. Effect of Grignard to Ketone Ratio on Products from the Reaction of "CH_3MgBr"[a] with 2-Methylbenzophenone in Ether at Room Temperature.

["CH_3MgBr"] (moles/li)	[2-MBP] (moles/li)	$\frac{["CH_3MgBr"]}{[2\text{-MBP}]}$	% Yield Ketone[b]	1,2-Addition[c]	Pinacol[d]	Hydrol[e]	[Hydrol[3]] (moles/li)
0.010	0.99	1:99	xs	100	0	0	0
0.010	0.11	1:11	xs	100	0	0	0
1.50	1.50	1:1	0	100	0	0	0
1.50	0.15	10:1	0	99	0.6	Trace	Trace
1.50	0.015	100:1	0	89	2	9	0.00135
1.50	0.00375	400:1	0	62	2	36	0.00135
1.50	0.001875	800:1	0	40	4	56	0.00105

a. Prepared from doubly sublimed magnesium using excess magnesium.

b. 2-methylbenzophenone.

c. 1-phenyl-1-(2-methylphenyl) ethanol.

d. 2,2'-dimethylbenzopinacol.

3. 2-methylbenzhydrol.

Table 12. Formation of Products with Respect to Time in the Reaction of "CH_3MgBr"[a] (0.50 M) with 2-Methylbenzophenone (0.0125 M) in Et_2O at -30"[b].

	% Yield				
Rx Time	Unreacted Ketone (%)	1,2-Addition[c]	Pinacol[d]	2-Methyl-benzhydrol	Hydrol/Addition
10 sec	68	2.7	1.7	28	10.4
1 hr	46	18	2.0	34	1.9
4 hr	10	48	2.3	39	0.81
12 hr	0	56	2.5	41	0.73

a. Prepared from doubly sublimed magnesium using excess magnesium.

b. Analysis by NMR.

c. 1-phenyl-1-(2-methylphenyl) ethanol.

d. 2,2'-dimethylbenzopinacol.

Table 13. Formation of 2-Methylbenzhydrol at 400:1 Grignard to Ketone Ratio

Grignard[a] Formed In	Reaction Carried Out In	% Yield Reduction Product[b] $C_6H_5(C_7H_7)CHOH$	% Yield Reduction Product[b] $C_6H_5(C_7H_7)CDOH$
$CH_3CH_2OCH_2CH_3$	$CH_3CH_2OCH_2CH_3$	59	-
$CH_3CD_2OCD_2CH_3$	$CH_3CD_2OCD_2CH_3$	0	27
$CH_3CH_2OCH_2CH_3$	$CH_3CD_2OCD_2CH_3$	65	0

a. CH_3MgBr prepared from Dow doubly sublimed magnesium.

b. Normalized as: % 1,2-addition + % reduction = 100%.

Table 14. Selectivity of Reduction of an Equalmolar Mixture of 2-Methylbenzophenone and Acetone with "CH_3MgBr" and "CH_3MgBr" + MgH_2.[a]

Grade of Magnesium Used To Prepare "CH_3MgBr"	1,2-Addition[b] Products (%)	Reduction Products (%)[b]	
		2-Methylbenzhydrol	Isopropanol
Dow (DS)	74.5	25.0	0.5
ROC/RIC[c]	100.0	0	0
ROC/RIC[c] + MgH_2	74.0	24.5	1.5

a. Millimoles of each ketone = 0.3; mmole CH_3MgBr = 120; mmole MgH_2 = 0.2.

b. Yields normalized as: % 1,2-addition + % reduction = 100%.

c. Grignard prepared in excess CH_3Br.

Table 15. Stereochemistry of Reduction of 4-tert-butycyclohexanone (0.3 mmole) with "CH_3MgBr" (120 mmole) and "CH_3MgBr" + MgH_2.

		Alkylation (%)			Reduction (%)		
Grade Mg Used	mmoles MgH_2	Total[a]	Axial[b] Alcohol	Equatorial[b] Alcohol	Total[a]	Axial[b] Alcohol	Equatorial[b] Alcohol
Dow (DS)	0	84	66	34	16	11	89
ROC/RIC[c]	0	100	59	41	0	-	-
ROC/RIC[c]	0.2	92	62	38	8	21	79
--------	0.3	-	-	-	-	68	32

a. Normalized as: % alkylation alcohols + % reduction alcohols = 100%.

b. Normalized as: % axial alcohol + % equatorial alcohol = 100%.

c. Grignard prepared in excess CH_3Br.

Table 16. Effect of the Size of Magnesium Shavings and Methyl Bromide Flow Rate on the Percentage of 2-Methylbenzhydrol in Reactions Involving 1.5 M Methylmagnesium Bromide[a] with 0.00375 M 2-Methylbenzophenone.

Mg Shaving Size	Flow Rate (cc/min)	% Yield[b] 1,2-Addition	Pinacol	Hydrol
Fine	214[c]	41	ND	59
Fine	682[d]	74	ND	27
Medium	682[d]	84	ND	16
Large	682[d]	91	ND	9

a. All preparations utilized 28 g of Dow doubly sublimed magnesium.

b. Normalized as: % 2-methylbenzhydrol + % 1,2-addition = 100%.

c. Flow time = 85 minutes.

d. Flow time = 28 minutes.

Table 17. Products of the Reaction of "CH_3MgBr" (0.600 M) in the Presence of "Trapping Agents" (0.100 M) in Diethylether at Room Temperature[a].

Exp.	Trapping Agent	[2-MBP] M	% $FeCl_3$	% Pinacol[c]	% Addition	% Recovered 2-MBP	% Recovered Trap
1	Styrene	0	0	-	-	-	76.1[d]
2	Styrene	0	1.73	-	-	-	26.8[d]
3	Styrene	0.100	0	0	100	0	67.0[d]
4	Styrene	0.100	1.73	94.7	5.3	0	27.1[d]
5	pDNB[b]	0	0	-	-	-	57.0
6	pDNB	0	1.73	-	-	-	47.6
7	pDNB	0.100	0	0	96.3	3.7	43.1
8	pDNB	0.100	1.73	39.6	23.6	36.8	33.3
9	None	0.100	0	0	100	0	-
10	None	0.100	1.73	96.3	3.7	0	-

a. Reaction Time = 3 hours.

b. p-Dinitrobenzene.

c. Normalized: 100% = % Pinacol + % 1,2-Addition.

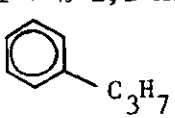
d. No products corresponding to  .

Table 18. Products from the Reaction of Grignard Reagents with 2,2'-Dimethylbenzopinacol in the Presence or Absence of p-Dinitrobenzene (p-DNB).

Exp.	Grignard Reagent	[Grignard]	[Pinacol]	[p-DNB]	Rx Time (hrs.)	PRODUCTS[a] % 1,2-Addn.	% Pinacol	% Ketone	% Hydrol	% p-DNB Recovered
1	tBuMgCl	0.300 M	0.013 M	0	70	0	100	0	0	-
2	CH_3MgBr	0.300 M	0.013 M	0	70	0	100	0	0	-
3	CH_3MgBr	0.050 M	0.025 M	0.050 M	3	0	72.6	27.4	0	79.2
4	CH_3MgBr	0.300 M	0.025 M	0.050 M	3	42.4	51.2	6.3	0	12.3

a. Normalized: 100% = % 1,2-Addition + % Pinacol + Ketone + % Hydrol + % Ketone.

Table 19. Products from the Reaction of Grignard Reagents Which Have Been in Contact With p-Dinitrobenzene (p-DNB) for 30 Minutes Prior to Addition of 2-MBP in Diethylether at Room Temperature.

Exp.	Grignard Reagent	[R-MgX] M	[p-DNB] M	[2-MBP] M	Products[a] % 1,2-Addn.	% Pinacol	% 1,6-Addn.	% Ketone	% Rec'd p-DNB	RMgX[b] / p-DNB Used
1[c]	CH_3MgBr	0.287	0.048	0.048	100	0	0	0	36.7	----
2[d]	CH_3MgBr	0.092	0.015	0.092	56.6	0	0	43.4	26.9	3.56
3[c]	t-BuMgCl	0.287	0.048	0.048	14.3	0	∿77.2	∿ 8.5	4.9	5.77
4[d]	t-BuMgCl	0.092	0.015	0.092	1.4	0	∿ 4.1	∿94.6	0.0	5.68

a. Normalized: 100% = 1,2-Addition + % Pinacol + % 1,6-Addition + % Ketone.

b. Mmoles of Grignard reagent used, but not accountable in products divided by mmoles of p-DNB used.

c. Reaction time = 3 hours.

d. Reaction time = 21 hours.

Table 20. Products From the Reaction of "CH_3MgBr"[a] With 2-MBP (0.0167 M) in the Presence or Absence of p-Dinitrobenzene (p-DNB) in Diethylether at Room Temperature: A Pseudo-Kinetic Study.

Exp.	["CH_3MgBr"]	% p-DNB	Reaction Time (mins)	% 1,2-Addn.[b]	% Pinacol	% Recovered Ketone	% Recovered p-DNB
1	0.033 M[c]	0	3	23.9	Trace	76.1	-
2	0.033 M	0	9	41.4	4.1	54.9	-
3	0.033 M	0	16	58.6	10.5	31.0	-
4	0.033 M	0	30	63.9	13.1	23.0	-
5	0.100 M	17	5	57.2	0	42.8	17.8
6	0.100 M	17	11	79.6	0	20.4	15.6
7	0.100 M	17	20	91.9	0	8.1	19.4
8	0.100 M	17	40	98.7	0	1.3	13.9

a. Dow doubly sublimed magnesium, but obviously contaminated by a few ppm $FeCl_3$ or other transition metal salt.

b. Normalized as 100% = % 1,2-Addition + % Pinacol + % Ketone.

c. This provides about the same Grignard Concentration as exists in the p-DNB doped reactions considering how much is used up in the reaction with the p-DNB.

Table 21. Products From the Reaction of "t-BuMgCl" With 2-MBP (0.0167 M) in the Presence or Absence of p-DNB in Diethylether at Room Temperature.

Exp.	["t-BuMgCl"]	% p-DNB	Reaction Time (mins)	% 1,6-Addn.[a]	% 1,2-Addn.	% Pinacol	% Recovered Ketone	% Recovered p-DNB
1	0.033 M[b]	0	3	71.2(78.4)[c]	19.6(21.6)	9.1	0	-
2	0.033 M	0	6	76.4(83.7)	14.9(16.3)	8.7	0	-
3	0.033 M	0	9	73.5(79.7)	18.7(20.3)	7.8	0	-
4	0.033 M	0	18	74.2(83.5)	14.7(16.5)	11.2	0	-
5	0.133 M	12.5	4	83.0	17.0	0	0	0
6	0.133 M	12.5	7	84.3	15.7	0	0	3.1
7	0.133 M	12.5	16	84.0	16.0	0	0	4.6
8	0.133 M	12.5	29	85.0	15.0	0	0	10.5

a. Normalized 100% = % 1,6-Addition + % 1,2-Addition + % Pinacol + % Ketone.

b. Provides the same effective Grignard concentration considering the reaction between "tBuMgCl" and p-DNB.

c. Normalized 100% = % 1,6-Addition + % 1,2-Addition.

Table 22. The Reaction of "CH_3MgBr" (0.150 M) with 2-MBP or Benzophenone (0.100 M) in the Presence of Various Amounts of $FeCl_3$ in Diethylether at Room Temperature for 3 Hours.

Exp.	Ketone	ppm $FeCl_3$	% 1,2-Addition[a]	% Pinacol
1	2-MBP	4,000	45.3	54.7
2	2-MBP	40,000	23.7	76.3
3	$Ph_2C=O$	4,000	56.8	43.2
4	$Ph_2C=O$	40,000	30.6	69.4

a. Normalized 100% = % 1,2-Addition + % Pinacol.

Table 23. Product From the Reaction of Grignard Reagents (0.940 mmoles) With Fluorenone (0.627 mmoles) in Diethylether (5.00 ml) for 4 Hours.

Exp.	Grignard Reagent	ml HMPA added	ppm $FeCl_3$	% 1,2-Addn.[c]	% 1,6-Addn.	% Pinacol	% Hydrol
1	CH_3MgBr[a]	0	0	100	0	0	0
2	CH_3MgBr	0	4000	76.5	0	29.4	0
3	CH_3MgBr	5	0	99.2	0	0.8	0
4	tBuMgCl[b]	0	0	74.8	15.4	9.8	0
5	tBuMgCl	0	4000	75.8	13.2	11.0	0
6	tBuMgCl	5	0	93.6	6.4	0	0

a. CH_3MgBr prepared from excess Magnesium (Ventron Chips; 99.99%)

b. t-BuMgCl prepared from 1:1 t-BuCl: Magnesium (Ventron Chips; 99.99%)

c. Normalized: 100% = % 1,2-Addition + % 1,6-Addition + % Pinacol + % Hydrol

Table 24. Products From the Reaction of Grignard Reagents (0.093 M) With Acetone (0.063 M) in Diethylether at Room Temperature

Exp.	Grignard Reagent	Grade of Mg[a]	ppm $FeCl_3$	Reaction Time	% 1,2-Addn.	% Reduction	% Pinacol	% Acetone[c]
1	CH_3MgBr	GGT[b]	0	20 mins	100	0	0	0
2	CH_3MgBr	49's[c]	0	20 mins	100	0	0	0
3	CH_3MgBr	D.S.[b]	0	20 mins	100	0	0	0
4	CH_3MgBr	GGT	4000	20 mins	100	0	0	0
5	CH_3MgBr	49's	4000	20 mins	100	0	0	0
6	CH_3MgBr	D.S.	4000	20 mins	100	0	0	0
7	t-BuMgCl[d]	GGT	0	20 mins	55.6	15.7	0	28.7
8	t-BuMgCl	D.S.	0	20 mins	62.1	8.4	0	29.5
9	t-BuMgCl	GGT	4000	20 mins	5.1	87.8	0	7.1
10	t-BuMgCl	D.S.	4000	20 mins	17.1	73.9	0	9.0
11	t-BuMgCl	D.S.	0	10 secs	20.4	0.5	0	79.2
12	t-BuMgCl	D.S.	0	21 secs	28.4	2.4	0	69.2
13	t-BuMgCl	D.S.	0	50 secs	37.6	3.2	0	59.1
14	t-BuMgCl	D.S.	0	60 secs	40.4	4.6	0	55.0
15	t-BuMgCl	D.S.	0	120 secs	49.7	4.4	0	45.9
16	t-BuMgCl	D.S.	4000	6 secs	12.3	23.3	0	64.4
17	t-BuMgCl	D.S.	4000	9 secs	11.8	28.1	0	60.0
18	t-BuMgCl	D.S.	4000	28 secs	18.1	62.3	0	19.7
19	t-BuMgCl	D.S.	4000	60 secs	16.0	74.0	0	10.0
20	t-BuMgCl	D.S.	4000	120 secs	17.9	76.2	0	5.9

a. GGT = Grignard Grade Turnings; 49's = Ventron Chips (99.9%); D.S. = Dow, Doubly Sublimed.
b. Made from excess magnesium. c. Made from excess CH_3Br. d. All t-BuMgCl reagents made from 1:1 magnesium: t-BuCl. e. In 20 mins reactions this corresponds to % Enolization. In shorter reactions it also includes unreacted Ketone.

Table 25. Products From the Reaction of Various Magnesium Compounds (0.050 M) With "cis-Enone" (0.10 M) in Diethylether at Room Temperature: A Qualitative Rate Study.

			Enone[a]		Products[b]				
Exp.	R-Mg-X	Rxn Time (mins)	% cis	% trans	% 1,4-Addn.	% 1,2-trans-addn.	% 1,2-cis-Addn.	% 1,2-Redn.	% Rxn.
1	CH_3MgBr[c]	10	85.2	14.8	41.2	40.0	18.8	0	100
2	CH_3MgBr	20	83.7	16.3	45.7	40.7	13.6	0	100
3	CH_3MgBr	30	81.3	18.7	51.2	40.3	8.4	0	100
4	t-BuMgCl[d]	10	2.8	97.2	9.2	30.5	3.7	56.6	100
5	t-BuMgCl	20	3.7	96.3	8.8	26.5	1.6	63.1	100
6	t-BuMgCl	30	3.7	96.3	10.5	25.5	0.8	63.2	100
7	$MgBr_2$[d]	10	96.3	3.7	-	-	-	-	3.7
8	$MgBr_2$	20	93.0	7.0	-	-	-	-	7.0
9	$MgBr_2$	30	88.7	11.3	-	-	-	-	11.3
10	$MgBr_2$	100	80.9	19.1	-	-	-	-	19.1
11	$(CH_3)_2Mg$[d]	10	98.4	1.6	9.4	15.0	75.6	0	100
12	$(CH_3)_2Mg$	20	98.5	1.5	13.2	26.7	60.0	0	100
13	$(CH_3)_2Mg$	30	98.7	1.3	16.5	31.4	52.2	0	100
14	BLANK	30	99.7	0.3	-	-	-	-	-

a. Normalized: 100% = % "cis-Enone" + % "trans-Enone". b. Normalized: 100% = % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition + % 1,2-Reduction. c. Made from Dow, doubly sublimed magnesium using excess CH_3Br. d. Made from Dow, doubly sublimed magnesium.

Table 26. Products of the Reaction of Grignard Reagents (0.033 M) With "cis- and trans-enone" (0.0667 M) in Diethylether at Room Temperature for Twenty Minutes.

					Starting Enone[b]				Products[c]	
Exp.	Grignard Reagent	Grade[a] of Mg	ppm $FeCl_3$	Enone[b] (Purity)	% cis	% trans	% 1,4-Addn.	% 1,2-trans-Addn.	% 1,2-cis-Addn.	% 1,2-Reduction
1	CH_3MgBr	Stork	0	cis(99.5%)	88.8	11.2	55.0	35.2	9.0	0
2	CH_3MgBr	GGT	0	cis(99.2%)	83.8	16.2	47.7	40.2	12.0	0
3	CH_3MgBr	D.S.	0	trans(100%)	0	100.0	51.4	48.6	0	0
4	CH_3MgBr	D.S.	0	cis(99.2%)	83.1	16.7	40.9	40.2	18.9	0
5	CH_3MgBr	D.S.	400	cis(99.2%)	73.7	26.3	48.4	44.6	6.9	0
6	CH_3MgBr	D.S.	4,000	cis(99.2%)	39.3	60.7	48.4	50.4	1.2	0
7	CH_3MgBr	D.S.	40,000	cis(99.2%)	12.4	87.6	46.7	53.2	0.1	0
8	t-BuMgCl	GGT	0	cis(99.2%)	6.2	93.8	10.2	26.5	3.7	59.7
9	t-BuMgCl	D.S.	0	cis(99.2%)	4.0	96.0	11.9	25.3	3.1	59.7[d]
10	t-BuMgCl	D.S.	40,000	cis(99.2%	6.5	93.5	9.1	24.4	0.5	66.0
11	t-BuMgCl	D.S.	0	trans(100%)	2.3	97.7	15.9	33.9	0	50.2[d]
12	AllylMgBr	D.S.	0	cis(99.7%)	99.2	0.8	0	0.7	99.3	Trace
13	AllylMgBr	D.S.	40,000	cis(99.6%)	24.5	75.5	0	4.0	96.0	Trace
14	AllylMgBr	D.S.	0	trans(100%)	0	100.0	0	100.0	0	Trace
15	$MgBr_2$	D.S.	0	cis(99.7%)	93.0	7.0	-	-	-	-
16	-	-	40,000	cis(99.7%)	99.7	0.3	-	-	-	-

a. GGT = Grignard Grade Turnings; D.S. = Dow, Doubly sublimed magnesium.

b. Normalized: 100% = % "cis-enone" + % "trans-enone".

c. Normalized: 100% = % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition + % 1,2-Reduction

d. Shown to be 100% trans by glc on TCEP.

Table 27. Products From the Reactions of "CH_3MgBr" (0.025 M) With "cis- and trans-Enone" (0.025 M) in Diethylether at Room Temperature: Rate Study With Time.

			Enone[a]		Products[a]		
Exp.	Enone	Reaction Time (secs)	% cis	% trans	% 1,4-Addition	% 1,2-trans-Addition	% 1,2-cis-Addition
1	cis[b]	10	99.7	0	0.02	0.2	0.01
2	cis	29	98.2	0	0.4	0.9	0.4
3	cis	60	97.9	0	0.7	0.7	0.7
4	cis	120	89.2	0	4.2	3.1	3.5
5	cis	240	78.5	0	8.1	5.3	8.1
6	cis	300	63.4	0	17.1	13.0	6.5
7	cis	600	40.1	0	27.8	22.5	9.6
8	cis	1200	22.7	0	35.6	30.2	11.5
9	trans	10	0	51.9	25.3	23.0	0
10	trans	34	0	22.6	41.0	36.3	0
11	trans	60	0	16.8	43.6	39.8	0
12	trans	120	0	6.8	47.8	45.3	0
13	trans	240	0	2.0	49.7	48.4	0

a. Normalized: 100% = % "cis-Enone" + % "trans-Enone" + % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition. b. Blank run demonstrated "cis-Enone" to be 99.3% cis- and 0.7% trans-isomer.

Table 28. Products of the Reactions of Various Organolithium Compounds (0.0333 M) With "cis- and trans-enone" (0.0667 M) in Diethylether at Room Temperature.[a]

Exp.	R-M	Enone[b] (Purity)	Enone[b] ppm $FeCl_3$	Enone[b] % cis	Enone[b] % trans	Products[c] % 1,4-Addn.	Products[c] % 1,2-trans-Addn.	Products[c] % 1,2-cis-Addn.	Products[c] % 1,2-Reduction
1	MeLi	cis(99.5%)	0	98.7	1.3	0	1.3	98.7	0
2	MeLi	cis(99.5%)	40,000	60.3	39.7	0	25.0	75.0	0
3	MeLi	trans(100%)	0	0	100.0	0	100.0	0	0
4	MeLi	cis(87.0%)	0	89.0	11.0	0	17.7	82.3	0
5	$LiCuMe_2$	cis(99.7%)	0	0.2	99.8	100	0	0	0
6	$LiCuMe_2$	cis(99.7%)	40,000	0	100.0	100	0	0	0
7	$LiCuMe_2$	trans(100%)	0	0	100.0	100	0	0	0
8	(4 MeLi + CuI)[d]	cis(99.7%)	0	2.2	97.8	31.3	10.1	58.5	0
9	(4 MeLi + CuI)[d]	trans(100%)	0	0	100.0	40.1	59.9	0	0
10	$LiCu_2Me_3$[e]	cis(99.3%)	0	0	100.0	100	0	0	0
11	$LiCu_2Me_3$[e]	trans(100%)	0	0	100.0	100	0	0	0
12	t-BuLi[f]	cis(99.3%)	0	63.2	36.8	7.0	6.8	85.6	0.7
13	t-BuLi	cis(99.5%)	40,000	40.6	59.4	2.0	5.4	92.0	0.6
14	t-BuLi	trans(100%)	0	3.9	96.1	46.9	51.2	0	1.9

a. Reaction time 20 minutes.

b. Normalized 100% = % cis + % trans.

c. Normalized 100% = % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition + % 1,2-Reduction.

d. 0.013 M. e. 0.020 M in THF. f. 0.0667 M.

Table 29. Products of the Reactions of Organometallic Compounds (0.033 M) With "cis- and trans-enone" (0.0667 M) at Room Temperature.[a]

Exp.	R-M	Enone[b] % (Purity)	Solvent	Enone[b] ppm $FeCl_3$	Enone[b] % cis	Enone[b] % trans	Products[c] % 1,4-Addn.	Products[c] % 1,2-trans-Addn.	Products[c] % 1,2-cis-Addn.	Products[c] % 1,2-Reduction	% Reaction[f]
1	Me_2Mg	cis(99.8)	Ether	0	98.9	1.1	5.0	6.5	88.5	0	100
2	Me_2Mg[e]	cis(87.3)	Ether	40,000	75.0	25.0	47.3	52.3	0.4	0	100
3	Me_2Mg[e]	trans (98)	Ether	0	1.4	98.6	50.3	49.7	0	0	100
4	Me_3Al	cis(99.7)	Ether	0	98.8	1.2	0	100	0	0	0.3
5	Me_3Al	cis(99.7)	Ether	40,000	73.0	27.0	15.3	84.7	0	0	17.0
6	Me_3Al	trans(100)	Ether	0	0	100	12.2	87.8	0	0	45.8
7	Me_3Al	trans(100)	Ether	40,000	0	100	20.4	79.6	0	0	45.0
8	Me_3Al	cis(75.0)	Benzene	0	64.7	35.3	28.5	38.5	33.1	0	47.8
9	Me_3Al	cis(75.0)	Benzene	40,000	36.0	64.0	41.0	46.5	12.5	0	66.0
10	Me_3Al	trans (98)	Benzene	0	2.7	97.3	29.4	70.6	0	0	59.8
11	Me_3Al	trans (98)	Benzene	40,000	0	100	34.3	65.7	0	0	76.6
12	Me_2AlCl	cis(75.0)	Benzene	0	0	100	48.8	41.5	9.8	0	8.2
13	Me_2AlCl	cis(75.0)	Benzene	40,000	0	100	58.3	41.7	0	0	4.8

The following compounds failed to effect any changes in the starting enone ("cis- or trans-") after 46 hours in either ether or benzene in the presence or absence of 40,000 ppm $FeCl_3$: Me_2Zn, MeZnBr, t-Bu_2Zn.

a. Reaction Times: 46 hrs. in Ether; 44 hrs. in Benzene; 20 mins. for Me_2Mg reactions. b. Normalized: 100% = "cis-enone" + % "trans-enone". c. Normalized: 100% = % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition + % 1,2-Reduction. d. 0.103 M. e. 0.0167 M. f. Based on organometallic.

Table 30. Products of the Reactions of Organometallic Reagents (0.0333 M) With "cis- and trans-enone" (0.0667 M) in the presence of pDNB in Diethylether at Room Temperature.

				Starting Enone[a]			Products[b]				
Exp.	R-M	% pDNB	Reaction Time	Enone % (Purity)	% cis	% trans	% 1,4-Addn.	% 1,2-trans-Addn.	% 1,2-cis-Addn.	% 1,2-Reduction	%[c] Reaction
1	CH_3MgBr	20	20 mins	cis(98.7)	96.4	3.6	44.8	37.2	17.9	0	45
2	CH_3MgBr	20	3 hrs	cis(98.7)	95.3	4.7	47.3	38.6	14.0	0	41
3	CH_3MgBr	20	19 hrs	cis(98.7)	93.9	6.1	48.2	40.6	11.2	0	56
4	CH_3MgBr	30	20 mins	cis(99.3)	100	0.04	16.1	13.3	70.6	0	42
5	CH_3MgBr	100	20 mins	cis(99.2)	98.7	1.3	Trace	Trace	Trace	0	0.1
6	t-BuMgCl	5	20 mins	cis(98.7)	3.5	96.5	13.7	14.0	1.3	71.1	60
7	t-BuMgCl	20	20 mins	cis(87.3)	84.2	15.8	0	0	0	0.2	0.2
8	t-BuMgCl	100	20 mins	cis(87.3)	86.0	14.0	0	0	0	0	0
9	AllylMgBr	20	20 mins	cis(99.6)	97.9	2.1	0	2.5	97.5	Trace	100
10	AllylMgBr	100	20 mins	cis(99.6)	98.0	2.0	0	2.4	97.6	Trace	100
11	$LiCuMe_2$	20	15 mins	trans(100)	0	100	100	0	0	0	7.1
12	$LiCuMe_2$	100	15 mins	trans(100)	0	100	100	0	0	0	40

a. Normalized % "cis-enone" + % "trans-enone" = 100%.

b. Normalized % 1,4-Addition + % 1,2-trans-Addition + % 1,2-cis-Addition + % 1,2-Reduction = 100%.

c. Based on Organometallic reagent.

REFERENCES AND NOTES

1. E. C. Ashby, H. M. Neumann and J. T. Laemmle, Accts. of Chem. Res., 7, 272 (1974).

2. E. C. Ashby, J. Laemmle and M. H. Neumann, J. Am. Chem. Soc., 94, 5421 (1972).

3. E. C. Ashby, Li-Chung Chao, and H. M. Neumann, J. Am. Chem. Soc., 95, 4896 (1973).

4. J. F. Fauvarque and E. Rouget, C. R. Acad. Sci. Ser. C, 267, 1355 (1968).

5. C. Blomberg, R. M. Sallinger and H. S. Mosher, J. Org. Chem., 34, 2385 (1969).

6. T. Holm and I. Crossland, Acta Chem. Scand., 25, 59 (1971).

7. a. E. C. Ashby, F. Walker and H. M. Neumann, Chem. Commun., 330 (1970).
   b. E. C. Ashby, H. M. Neumann, F. W. Walker, J. Laemmle and L. C. Chao, J. Am. Chem. Soc., 95, 3330 (1973).

8. H. C. Brown and H. L. Young, J. Org. Chem., 22, 719 (1957).

9. C. S. Marvel and W. M. Sperry, Org. Syntheses, Coll. Vol. I, 95 (1941).

10. J. A. Riddick and W. B. Bunger, "Organic Solvents: Techniques in Organic Chemistry," 3rd ed., Wiley-Interscience, New York, N.Y., 1970, p. 242.

11. L. Schnerling, J. Am. Chem. Soc., 69, 1121 (1947).

12. A. Jeans and R. Adams, J. Am. Chem. Soc., 59, 2608 (1937).

13. N. P. Bui-Hoi, N. Hoan, J. LeCocgr, and M. DeClercq, Recueil des Travaux Chemiques des Pays-Bas et de la Belgique, 67, 795 (1948).

14. S. T. Bowden and T. L. Thomas, J. Chem. Soc. London, 1242 (1940).

15. A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Longman's, London, 1959, p. 535.

16. J. F. Norris and A. W. Olmsted, Org. Syntheses, Coll. Vol. I., 144 (1941).

17. O. Kamm and C. S. Marvel, Org. Syntheses, 1, 3 (1921).

18. E. Rothstein and R. W. Saville, J. Chem. Soc., London, 1956 (1949).

19. L. F. Fieser and C. C. Price, J. Am. Chem. Soc., 58, 1838 (1936).

20. H. A. Smith and J. A. Stanfield, J. Am. Chem. Soc., 71, 81 (1949).

21. F. E. Pounder and I. Masson, J. Chem. Soc., London, 1357 (1934).

22. J. Laemmle, E. C. Ashby and H. M. Neumann, J. Am. Chem. Soc., 93, 5120 (1971).

23. E. C. Ashby and R. G. Beach, Inorg. Chem., 9, 2300 (1970).

24. R. Adams and E. W. Adams, Organic Syntheses, Coll. Vol. I., 459 (1941).

25. M. S. Karasch and S. Weinhouse, J. Org. Chem., 1, 209 (1936).

26. E. D. Hughes, C. K. Ingold, and N. A. Taher, J. Chem. Soc., London, 949 (1940).

27. M. Protiva and M. Borovicua, Collection of Czechoslovak Chemical Communications, 13, 582 (1948).

28. J. C. Bailar, Jr., J. Am. Chem. Soc., 52, 3596 (1930).

29. G. Edgar, G. Calingaert and R. E. Marker, J. Am. Chem. Soc., 51, 1483 (1929).

30. Analyzed by: Atlantic Microlab, Inc., P.O. Box 54306, Atlanta, Ga. 30308.

31. E. C. Ashby and R. D. Schwartz, J. Chem. Educ., 51, 65 (1974).

32. E. C. Ashby and R. Beach, Inorg. Chem., 10, 906 (1971).

33. NMR δ values were obtained through private communication with Torkil Holm, The Technical Institute of Denmark.

34. These experiments were carried out primarily by Dr. Jerry D. Buhler.

35. These experiments were carried out primarily by Joe S. Bowers, Jr. and Joe T. Laemmle.

36. The "other" product is believed to be 1-(2,6-dimethylphenyl)-1-phenyl ethanol. NMR and mass spectral analysis are consistent with this structure. An attempted independent synthesis of this compound gave a mixture of products, one of which appears to be identical with the "other". This product does not occur at normal Grignard/ketone ratios and will be treated only briefly in this thesis.

37. F. Daniel Miller, "Time Sharing System Applications in the Decision Sciences," Department of Quantitative Methods, Georgia State University, June, 1974, p. 43.

38. The "index of determination" is the explained variance divided by the total variance or % explained variance/100.

39. It is not necessary, nor likely that the active catalytic iron species is Fe(III). It may well be Fe(0) or Fe(I).

40. It is possible that even [Fe°] is the "active catalyst" since $Fe(CO_2)_5$ is almost as effective as $Fe(acac)_3$ in catalyzing pinacol formation. $Fe(CO)_5$ alone, however, or in the presence of trace amounts of "CH_3MgBr" has no effect on 2-MBP.

41. These experiments were carried out primarily by Irene A. Lopp and Jerry D. Buhler.

42. I. A. Lopp, J. D. Buhler and E. C. Ashby, J. Am. Chem. Soc., 97, 4966 (1975).

43. The half life for the disappearance of ketone in the noncatalyzed reaction was estimated from Figure II to be 9.3 hours. Since 1,2-addition was the only detectable product in this case, 9.3 hours represents the half life of the noncatalyzed addition reaction under these conditions. The rate constant calculated from the half life was: $k_{noncat} = 0.075\ sec^{-1}$. The half life for the disappearance of ketone in the reaction in which $FeCl_3$ had been added was estimated to be 1.8 hours corresponding to a rate constant, $k_{cat} = 0.39\ sec^{-1}$. Thus ketone disappears approximately five times as fast in the catalyzed case. A comparison in the two cases of the rate of 1,2-addition itself was made in the following fashion. From Table 6 the 1.5 ratio of 2,2'-dimethylbenzopinacol to 1,2-addition demonstrates that the rate constant leading to formation of pinacol, kp, is 1.5 times greater than the rate constant leading to 1,2-addition, $k_{1,2}$. Therefore: $kp = 1.5\ k_{1,2}$. The rate constant for the disappearance of ketone in the catalyzed case, k_{cat}, must equal to the sum of $kp + k_{1,2}$. Therefore:

$k_{cat} = kp + k_{1,2} = 1.5\ k_{1,2} + k_{1,2} = 2.5\ k_{1,2}$. The rate constant, then, for addition in the catalyzed case, $k_{1,2}$ is equal to k_{cat}/ 2.5 which is equal to 0.16 sec^{-1}. Thus, 1,2-addition itself is 2.1 (0.16 $sec.^{-1}$/0.075 $sec.^{-1}$) times as fast in the iron catalyzed reaction as in the noncatalyzed reaction.

44. Work in progress by other members of our team of investigators.

45. Other studies in this laboratory have shown that the kinetic product is also produced very early in reactions at room temperature, but conversion to thermodynamic pinacol occurs completely in less than 1 hr. (Work carried out by Daniel Campbell).

46. S. E. Rudolph and S. C. Smith, J. Chem. Soc., D, 1428 (1970).

47. Since reaction at Grignard:ketone ratio of 400 gives hydrol in 36 to 72% yield.

48. PPM trace elements in Dow doubly sublimed magnesium by spark source mass spectrometry: B-0.005, N-2.9, O-420, F-0.01, Na-8.9, Al-ND, Si-2, P-ND, S-1, Cl-25, K-0.85, Ca-1.8, Ti-ND, Cr-ND, Mn-ND, Fe-0.1, Co-ND, Cu-0.1, Zn-25, Ga-ND, Sr-ND, Y-ND, Zr-ND, Pb-ND. Analysis by MicroTrace Analytical Services, Industry, Calif. 91746 (ND = Not Detectable).

49. a. H. W. H. J. Bodewitz, C. Blomberg and F. Bickelhaupt, Tetrahedron, 31, 1053 (1975);
    b. Ibid, 719 (1973);
    c. H. M. Walborsky and A. E. Yound, J. Am. Chem. Soc., 86, 3288 (1964);
    d. H. M. Walborsky and M. S. Aronoff, J. Organometal. Chem., 51, 31 (1973).

50. N. Kornblum, Angew. Chem. Internat. Edit. Vol. 14, 11, 734 (1975).

51. C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, Inc., New York, N.Y., 1970, p. 184.

52. H. O. House, L. E. Huber, and M. J. Umen, J. Am. Chem. Soc., 94, 8471 (1972).

53. A. J. Fry, "Synthetic Organic Electrochemistry," Harper and Row, New York, N.Y., 1972, p. 123.

54. K. W. Bowers, et al., J. Am. Chem. Soc., 92, 2783 (1970).

55. H. O. House and Paul Weeks, J. Am. Chem. Soc., 97, 2770 (1975).

56. John Watkins, research group of Dr. E. C. Ashby, unpublished data.

57. H. O. House and P. D. Weeks, J. Am. Chem. Soc., 97, 2785 (1975).

58. a. E. S. Huyser, "Organic Reactive Intermediates: Free Radicals," ed. by S. P. McManus, Academic Press, New York, N.Y., 1973, p. 27.
b. R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed., Allyn and Bacon, Inc., Boston, Mass., 1966, p. 208.

59. D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N.Y., 1965, p. 9, p. 21.

VITA

Thomas Lee Wiesemann was born in Louisville, Kentucky on May 10, 1950 and attended both grammar and high school there.

His undergraduate work was done at Bellarmine College, Louisville, Kentucky, where he received a Bachelor of Arts degree in chemistry in 1972.

After a brief stay at Fort Jackson, South Carolina in basic training for the United States Army Reserves, Tom entered the Graduate program at the Georgia Institute of Technology, Atlanta, Georgia in 1972. Under the direction of Dr. E. C. Ashby, he received a Ph.D. in chemistry in 1977.

Tom is married to the former Martina Lynn Veigl and has been employed by the Union Camp Corporation, Princeton, New Jersey.